CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-972 / S-027
21-360 / S-014

Trade Name: Sustiva

Generic Name: (efavirenz)

Sponsor: Bristol Myers Squibb

Approval Date: March 28, 2006

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APPLICATION NUMBER:

20-972 / S-027
21-360 / S-014

CONTENTS

Reviews / Information Included in this NDA Review.	
Approval Letter	X
Approvable Letter	
Final Printed Labeling	**X**
Medical Review(s)	**X**
Chemistry Review(s)	
EA/FONSI	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/ Biopharmaceutics Review(s)	**X**
Administrative and Correspondence Document(s)	

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-360/S-014
NDA 20-972/S-027

Bristol-Myers Squibb Company
Attention: Lori A. DeVore
Associate Director
Global Regulatory Strategy
5 Research Parkway
Wallingford, CT 06492

Dear Ms. DeVore:

Please refer to your supplemental new drug application dated August 25, 2005, received August 26, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sustiva® (efavirenz) capsules and tablets.

We acknowledge receipt of your submissions dated September 22, 2005, February 9, 2006, February 23, 2006 and March 6, 2006.

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 and patient package insert submitted March 6, 2006).

Please submit an electronic version of the FPL 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 but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate these submissions "**FPL for approved supplement NDA 21-360/S-014" and "FPL for approved supplement NDA 20-972/S-027**." Approval of these submissions by FDA is not required before the labeling is used.

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
Food and Drug Administration
WO 22, Room 4447
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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, call Jaewon Hong, Regulatory Project Manager, at (301) 796-2013.

Sincerely,

{See appended electronic signature page}

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

Enclosure

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
3/28/2006 03:56:40 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-972 / S-027
21-360 / S-014

APPROVED LABELING

SUSTIVA®
(efavirenz) capsules and tablets

Rx only

DESCRIPTION

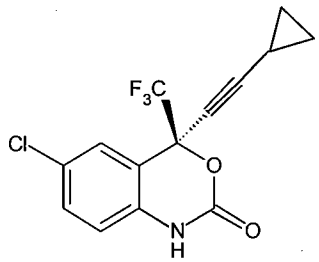
SUSTIVA® (efavirenz) is a human immunodeficiency virus type 1 (HIV-1) specific, non-nucleoside, reverse transcriptase inhibitor (NNRTI).

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 C_{max}, AUC, and C_{min} 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}, AUC, and C_{min}

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Coadministered Drug (mean % change) C_{max} (90% CI)	AUC (90% CI)	C_{min} (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%)	↓ 93% (90-95%)
	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%)	↑ 48%[a] (24-76%)
Indinavir	1000 mg q8h x 10 days	600 mg x 10 days	20			
	After morning dose			↔[b]	↓ 33%[b] (26-39%)	↓ 39%[b] (24-51%)
	After afternoon dose			↔[b]	↓ 37%[b] (26-46%)	↓ 52%[b] (47-57%)
	After evening dose			↓ 29%[b] (11-43%)	↓ 46%[b] (37-54%)	↓ 57%[b] (50-63%)
Lopinavir/ ritonavir	400/100 mg q12h x 9 days	600 mg x 9 days	11,7[c]	↔[d]	↓ 19%[d] (↓ 36-↑ 3%)	↓ 39%[d] (3-62%)
Nelfinavir	750 mg q8h x 7 days	600 mg x 7 days	10	↑ 21% (10-33%)	↑ 20% (8-34%)	↔

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

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Coadministered Drug (mean % change) C_{max} (90% CI)	AUC (90% CI)	C_{min} (90%CI)
Metabolite AG-1402				↓40% (30-48%)	↓37% (25-48%)	↓43% (21-59%)
Ritonavir	500 mg q12h x 8 days	600 mg x 10 days	11			
	After AM dose			↑24% (12-38%)	↑18% (6-33%)	↑42% (9-86%)[e]
	After PM dose			↔	↔	↑24% (3-50%)[e]
Saquinavir SGC[f]	1200 mg q8h x 10 days	600 mg x 10 days	12	↓50% (28-66%)	↓62% (45-74%)	↓56% (16-77%)[e]
Lamivudine	150 mg q12h x 14 days	600 mg x 14 days	9	↔	↔	↑265% (37-873%)
Tenofovir[g]	300 mg qd	600 mg x 14 days	29	↔	↔	↔
Zidovudine	300 mg q12h x 14 days	600 mg x 14 days	9	↔	↔	↑225% (43-640%)
Azithromycin	600 mg single dose	400 mg x 7 days	14	↑22% (4-42%)	↔	NA
Clarithromycin	500 mg q12h x 7 days	400 mg x 7 days	11	↓26% (15-35%)	↓39% (30-46%)	↓53% (42-63%)
14-OH metabolite				↑49% (32-69%)	↑34% (18-53%)	↑26% (9-45%)
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%)	↓45% (31-56%)
Voriconazole	400 mg po q12h x 1 day then 200 mg po q12h x 8 days	400 mg x 9 days	NA	↓61%[h]	↓77%[h]	NA
Carbamazepine	200 mg qd x 3 days, 200 mg bid x 3 days, then 400 mg qd x 29 days	600 mg x 14 days	12	↓20% (15-24%)	↓27% (20-33%)	↓35% (24-44%)
Epoxide metabolite				↔	↔	↓13% (↓30-↑7%)
Cetirizine	10 mg single dose	600 mg x 10 days	11	↓24% (18-30%)	↔	NA
Ethinyl estradiol	50 µg single dose	400 mg x 10 days	13	↔	↑37% (25-51%)	NA
Lorazepam	2 mg single dose	600 mg x 10 days	12	↑16% (2-32%)	↔	NA
Methadone	Stable maintenance 35-100 mg daily	600 mg x 14-21 days	11	↓45% (25-59%)	↓52% (33-66%)	NA
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%)	↓46% (31-58%)

↑ Indicates increase ↓ Indicates decrease ↔ Indicates no change or a mean increase or decrease of <10%.

[a] Compared with atazanavir 400 mg qd alone.

[b] Comparator dose of indinavir was 800 mg q8h x 10 days.

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

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

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Coadministered Drug (mean % change)		
				C_{max} (90% CI)	AUC (90% CI)	C_{min} (90%CI)

[d] Values are for lopinavir; the pharmacokinetics of ritonavir 100 mg q12h are unaffected by concurrent efavirenz.

[e] 95% CI.

[f] Soft Gelatin Capsule.

[g] Tenofovir disoproxil fumarate.

[h] 90% CI not available.

NA = not available.

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

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Efavirenz (mean % change)		
				C_{max} (90% CI)	AUC (90% CI)	C_{min} (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%)	↓ 16% (↓ 42-↑ 20%)
Nelfinavir	750 mg q8h x 7 days	600 mg x 7 days	10	↓ 12% (↓ 32-↑ 13%)[b]	↓ 12% (↓ 35-↑ 18%)[b]	↓ 21% (↓ 53-↑ 33%)
Ritonavir	500 mg q12h x 8 days	600 mg x 10 days	9	↑ 14% (4-26%)	↑ 21% (10-34%)	↑ 25% (7-46%)[b]
Saquinavir SGC[c]	1200 mg q8h x 10 days	600 mg x 10 days	13	↓ 13% (5-20%)	↓ 12% (4-19%)	↓ 14% (2-24%)[b]
Tenofovir[d]	300 mg qd	600 mg x 14 days	30	↔	↔	↔
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%)	↑ 22% (5-41%)
Rifabutin	300 mg qd x 14 days	600 mg x 14 days	11	↔	↔	↓ 12% (↓ 24-↑ 1%)
Rifampin	600 mg x 7 days	600 mg x 7 days	12	↓ 20% (11-28%)	↓ 26% (15-36%)	↓ 32% (15-46%)
Voriconazole	400 mg po q12h x 1 day then 200 mg po q12h x 8 days	400 mg x 9 days	NA	↑ 38%[e]	↑ 44%[e]	NA
Aluminum hydroxide 400 mg magnesium hydroxide 400 mg, plus simethicone 40 mg	30 mL single dose	400 mg single dose	17	↔	↔	NA
Carbamazepine	200 mg qd x 3 days, 200 mg bid x 3 days, then 400 mg qd x 15 days	600 mg x 35 days	14	↓ 21% (15-26%)	↓ 36% (32-40%)	↓ 47% (41-53%)

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

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Efavirenz (mean % change) C_{max} (90% CI)	AUC (90% CI)	C_{min} (90%CI)
Cetirizine	10 mg single dose	600 mg x 10 days	11	↔	↔	↔
Ethinyl estradiol	50 µg single dose	400 mg x 10 days	13	↔	↔	↔
Famotidine	40 mg single dose	400 mg single dose	17	↔	↔	NA
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%)	↔	↔

↑ Indicates increase ↓ Indicates decrease ↔ Indicates no change or a mean increase or decrease of <10%.

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

[b] 95% CI.

[c] Soft Gelatin Capsule.

[d] Tenofovir disoproxil fumarate.

[e] 90% CI not available.

NA = 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 n=422		SUSTIVA + IDV n=429		IDV + ZDV + LAM 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: **Pregnancy Category D.** Efavirenz may cause fetal harm when administered during the first trimester to a pregnant woman. 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 before initiation of SUSTIVA. If this drug is used during the first trimester of pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus.

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 2004, the Antiretroviral Pregnancy Registry has received prospective reports of 237 pregnancies exposed to efavirenz-containing regimens, nearly all of which were first-trimester exposures (232 pregnancies). Birth defects occurred in 5 of 188 live births (first-trimester exposure) and 0 of 13 live births (second/third-trimester exposure). None of these prospectively reported defects were neural tube defects. However, there have been four retrospective reports of findings consistent with neural tube defects, including meningomyelocele. All mothers were exposed to efavirenz-containing regimens in the first trimester. Although a causal relationship of these events to the use of SUSTIVA has not been established, similar defects have been observed in preclinical studies of efavirenz.

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.

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.

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 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 and phenobarbital, may require periodic monitoring of plasma levels (see **PRECAUTIONS: Drug Interactions**). 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 jiroveci* pneumonia [PCP], 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.

Women receiving SUSTIVA should be instructed to avoid pregnancy (see **WARNINGS: Reproductive Risk Potential**). 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. Women should be advised to notify their physician if they become pregnant while taking SUSTIVA. If this drug is used during the first trimester of pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential harm to the fetus.

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 Tables 5 and 6. The tables include potentially significant interactions, but are not all inclusive.

Table 5: Drugs That Are Contraindicated or Not Recommended for Use With SUSTIVA

Drug Class: Drug Name	Clinical Comment
Antifungal: voriconazole	CONTRAINDICATED because SUSTIVA significantly decreases voriconazole plasma concentrations, and coadministration may decrease the therapeutic effectiveness of voriconazole. Also, voriconazole significantly increases SUSTIVA plasma concentrations, which may increase the risk of SUSTIVA-associated side effects. See Tables 1 and 2.
Antihistamine: astemizole	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antimigraine: ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine)	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
Benzodiazepines: midazolam, triazolam	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

GI motility agent: cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
St. John's wort (*Hypericum perforatum*)	Expected to substantially decrease plasma levels of efavirenz; has not been studied in combination with SUSTIVA.

Table 6: Established[a] and Other Potentially Significant[b] Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect on Concentration of SUSTIVA or Concomitant Drug	Clinical Comment
Antiretroviral agents		
Protease inhibitor: Amprenavir	↓ amprenavir	SUSTIVA has the potential to decrease serum concentrations of amprenavir.
Protease inhibitor: Fosamprenavir calcium	↓ amprenavir	Fosamprenavir (unboosted): Appropriate doses of the combinations with respect to safety and efficacy have not been established. Fosamprenavir/ritonavir: An additional 100 mg/day (300 mg total) of ritonavir is recommended when SUSTIVA is administered with fosamprenavir/ritonavir once daily. No change in the ritonavir dose is required when SUSTIVA is administered with fosamprenavir plus ritonavir twice daily.
Protease inhibitor: Atazanavir	↓ atazanavir[a]	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.
Protease inhibitor: Indinavir	↓ indinavir[a]	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.
Protease inhibitor: Lopinavir/ritonavir	↓ lopinavir[a]	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.

Table 6: Established[a] and Other Potentially Significant[b] Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect on Concentration of SUSTIVA or Concomitant Drug	Clinical Comment
Protease inhibitor: Ritonavir	↑ ritonavir[a] ↑ efavirenz[a]	When ritonavir 500 mg q12h was coadministered with SUSTIVA 600 mg once daily, the 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.
Protease inhibitor: Saquinavir	↓ saquinavir[a]	Should not be used as sole protease inhibitor in combination with SUSTIVA.
Other agents		
Anticoagulant: Warfarin	↑ or ↓ warfarin	Plasma concentrations and effects potentially increased or decreased by SUSTIVA.
Anticonvulsants: Carbamazepine	↓ carbamazepine[a] ↓ efavirenz[a]	There are insufficient data to make a dose recommendation for efavirenz. Alternative anticonvulsant treatment should be used.
Phenytoin Phenobarbital	↓ anticonvulsant ↓ efavirenz	Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.
Antidepressant: Sertraline	↓ sertraline[a]	Increased in sertraline dose should be guided by clinical response.
Antifungals: Itraconazole Ketoconazole	↓ antifungal	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-infective: Clarithromycin	↓ clarithromycin[a] ↑ 14-OH metabolite[a]	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.
Antimycobacterial: Rifabutin	↓ rifabutin[a]	Increase daily dose of rifabutin by 50%. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week.

Table 6: Established[a] and Other Potentially Significant[b] Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect on Concentration of SUSTIVA or Concomitant Drug	Clinical Comment
Antimycobacterial: Rifampin	↓ efavirenz[a]	Clinical significance of reduced efavirenz concentrations is unknown.
HMG-CoA reductase inhibitors:		Plasma concentrations of atorvastatin, pravastatin, and simvastatin decreased. Consult the complete prescribing information for the HMG-CoA reductase inhibitor for guidance on individualizing the dose.
Atorvastatin	↓ atorvastatin	
Pravastatin	↓ pravastatin	
Simvastatin	↓ simvastatin	
Narcotic analgesic: Methadone	↓ methadone[a]	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.
Oral contraceptive: Ethinyl estradiol	↑ ethinyl estradiol[a]	Plasma concentrations increased by SUSTIVA; clinical significance unknown. 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.

[a] See **CLINICAL PHARMACOLOGY**, Tables 1 and 2 for magnitude of established interactions.
[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 (efavirenz) is given with the following: aluminum/magnesium hydroxide antacids, azithromycin, cetirizine, famotidine, fluconazole, lamivudine, lorazepam, nelfinavir, paroxetine, tenofovir disoproxil fumarate, 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 D: See **WARNINGS: Reproductive Risk Potential**.

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 8).

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 7 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 9.

Table 7: 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 8.

Table 8: 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 8, 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.

Pancreatitis has been reported, 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 9.

Table 9: 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, photoallergic dermatitis, 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 10.

Table 10: 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 11 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 11: 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® (efavirenz) 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 (efavirenz) 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

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Printed in USA

XX-XXXXXX-XX XXXXXXXXX Revised _____

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 (efavirenz).

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 the offspring of animals and women treated with SUSTIVA during pregnancy. It is not known whether SUSTIVA caused these defects. **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)
- Carbatrol®, Tegretol® (carbamazepine)

The following medicines may require a change in the dose of either SUSTIVA or the other medicine:

- The cholesterol-lowering medicines Lipitor® (atorvastatin), PRAVACHOL® (pravastatin), and Zocor® (simvastatin).
- Crixivan® (indinavir)
- Kaletra® (lopinavir/ritonavir)
- Methadone
- Mycobutin® (rifabutin)
- REYATAZ® (atazanavir sulfate). If you are taking SUSTIVA and REYATAZ, you should also be taking Norvir® (ritonavir).
- Rifadin® (rifampin) or the rifampin-containing medicines Rifamate® and Rifater®.
- 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 1-800-321-1335.

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Princeton, NJ 08543 USA

XX-XXXXXX-XX

XXXXXXXXX Revised _____

Based on package insert dated _____.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-972 / S-027
21-360 / S-014

MEDICAL REVIEW

Medical Officer Review
NDA 20972 SLR 027
NDA 21360 SLR014

Date of submission: August 25, 2005
Date MOR completed: February 27, 2006

Applicant: Bristol-Myers Squibb Company

Drug name: Efavirenz
Sustiva® (NDA 20-972 capsules; NDA 21-360 tablets)

Dosage and Administration: Oral
200 mg capsules; 600 mg tablets

Indications: Efavirenz in combination with other antiretroviral agents is indicated in the treatment of HIV-1 infection.

Resume
In this labeling supplement, the sponsor submitted proposed labeling changes to update the drug interactions tables in the label. Drug interactions tables have been revised to include Cmin values in Tables 1 and 2, and clinical comments have been added. Additional proposed changes to the current labeling include new data submitted to this Supplement, as well as information provided in the package labeling of atazanavir, lopinavir and voriconazole.

Recommendations
I concur with the recommendations of the Clinical Pharmacology Reviewer, Dr. Jen DiGiacinto, summarized as follows (see Clinical Pharmacology Review):

A. Rejection
1. The proposed labeling for the [redacted] is not acceptable and should be removed for the label.

B. Outstanding issues for which more data/discussion are necessary
1. The labeling revision proposed in Table 6 for fosamprenavir is not acceptable and should be revised to include similar information as listed in the Lexiva® label.
2. Please provide further discussion whether or not a dosing increase for efavirenz is warranted when coadministered with rifampin.
3. Please revise labeling for efavirenz and carbamazepine interaction to reflect that currently there is no supportive data for any dose adjustment for efavirenz when it's coadministered with carbamazepine and that an alternative anticonvulsant should be used.
4. The proposed labeling for the interaction between efavirenz and atorvastatin, simvastatin, and pravastatin is not justified. Please provide the assay information as requested in January 2006.

5. Please provide further justification, i.e., any *in vivo* data to support the addition of the potential interactions of efavirenz with pimozide and bepredil.
6. Please revise the information listing St. John's wort in Table 5 and remove it from Table 6.

C. Acceptable Revisions

1. All other proposed labeling revisions are acceptable, and may be incorporated in the Sustiva® label.

Regulatory Action: The application is approvable. Before these applications can be approved, however, the sponsor must submit revised draft labeling in response to the comments sent by facsimile on February 22, 2006.

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

Concurrences:
HFD-530/ATL/Struble
HFD-530/DD/Birnkrant

Cc: HFD-530/CSO/JHong
HFD-530/Clinical Pharmacology/DiGiacinto

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-972 / S-027
21-360 / S-014

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA:	21-360 (SLR014)/20-972 (SLR027)
Submission Date:	August 25, 2005
Brand Name:	SUSTIVA®
Generic Name:	Efavirenz
Formulation:	600 mg tablet/50-mg, 100-mg, and 200-mg capsules
Applicant:	Bristol-Myers Squibb Company
Reviewer:	Jennifer L. DiGiacinto, Pharm.D. (Note: Fellow Sarah Robertson, Pharm.D. contributed significantly to this review)
Team Leader:	Kellie S. Reynolds, Pharm.D.
OCP Division:	Division of Clinical Pharmacology 4
ORM Division:	Division of Antiviral Products

Table of Contents

	Page #
Review Information and Table of Contents	1
1. Executive Summary	1
Recommendation, Phase IV Commitments, and Summary	1
2. Labeling Recommendation	7
3. Individual Study Report Reviews	17
Carbamazepine	17
HMG-CoA Reductase Inhibitors	21
C_{min} Values of Efavirenz and Co-Administered Drugs	24
Rifampin	27

1. EXECUTIVE SUMMARY

In this labeling supplement, the Applicant has submitted proposed labeling changes to update the CLINICAL PHARMACOLOGY, PRECAUTIONS: Drug Interactions, and Patient Package Insert sections of the SUSTIVA package insert. In response to Agency correspondence from April 30, 2003, the presentation of drug interaction information has been revised to include C_{min} values in Tables 1 and 2 of CLINICAL PHARMACOLOGY. Also in response to this communication, the format of the tables in PRECAUTIONS: Drug Interactions has been revised to include a column for clinical comments. Additional proposed changes to the current labeling include new data submitted in this Supplement (interaction studies with carbamazepine, HMG-CoA reductase inhibitors, rifampin and indinavir/ritonavir) as well as information provided in the package labeling of atazanavir, lopinavir/ritonavir, fosamprenavir and voriconazole.

1.1 Recommendation

The change in C_{min} values of atazanavir, lopinavir/ritonavir, indinavir (unboosted), and co-administered efavirenz that have been added to Tables 1 and 2 of the CLINICAL PHARMACOLOGY section are from the prescribing information of Reyataz®, Kaletra®, and Crixivan®, respectively. The change in C_{min} values of fluconazole, clarithromycin (and hydroxy metabolite), lamivudine, zidovudine, nelfinavir (and metabolite AG-1402), ethinyl estradiol, cetirizine, azithromycin, and rifampin that have been added to the

tables are from previously submitted studies. The data from these studies were re-analyzed and the C_{min} values are reported in this submission. The results are reviewed in Section 3.1.3 and changes to the label are acceptable.

The change in C_{min} value of ritonavir is from study 266011, which was previously submitted as part of NDA 20972 is acceptable. Those of paroxetine, sertraline, rifabutin, and saquinavir are consistent with the findings of drug interaction studies 266106, 266109, and 266042 and 266036, respectively and are acceptable.

The "clinical comment" for voriconazole that has been added to Table 5 is taken from the Vfend® package insert.

The proposed labeling in Table 1 and Table 2 and the revised information to the Patient Information Leaflet for carbamazepine and efavirenz are acceptable. The proposed labeling for the efavirenz and carbamazepine interaction listed in Table 6 should be revised to reflect that currently there is no dose adjustment recommendation for efavirenz when coadministered with carbamazepine and an alternative anticonvulsant should be used.

The revised information to the Patient Information Leaflet regarding atorvastatin, simvastatin, and pravastatin is acceptable. The proposed labeling in Table 6 for atorvastatin, simvastatin, and pravastatin is acceptable. The proposed labeling for the interaction between efavirenz and atorvastatin, simvastatin, and pravastatin in Table 1 and Table 2 is not acceptable until we receive the assay information requested in our comments sent in January 2006. This PK information is reported in studies AI266919 and AI266927, which are included in the submission.

Currently there is a plethora of conflicting data in the literature regarding whether or not a dose increase for efavirenz (800-mg QD) is warranted when coadministered with rifampin. The applicant should review the current literature, including the journal article found in AIDS 2006 Jan 2; 20(1):131-2 and provide a justification for the proposed dose increase recommendation. The recommendation to increase the dose of EFV to 800 mg QD during co-administration with rifampin based on data from study DMP-266-029 and data from the recent Lopez-Cortez, et al. publication is not acceptable until further justification from the current literature is provided.

The labeling revision proposed in Table 6 for fosamprenavir (reference to LEXIVA label) is not acceptable and should be revised to include similar information to what is listed in the LEXIVA® label. An example of what is more acceptable would be language that includes the following:

a) Fosamprenavir (unboosted) -Appropriate doses of the combinations with respect to safety and efficacy have not been established.
b) Fosamprenavir/ritonavir- An additional 100 mg/day (300 mg total) of ritonavir is recommended when efavirenz is administered with LEXIVA/ritonavir once daily. No change in the ritonavir dose is required when efavirenz is administered with LEXIVA plus ritonavir twice daily.

The Applicant proposes to add information on the interaction between EFV and indinavir/ritonavir based on the publication by Aarnoutse et al. However, in order for this drug interaction data to be acceptable for inclusion in the label, the individual PK data and statistical analyses must be rerun by the Applicant and provided to the Agency in a

separate report. This comment was communicated to the Applicant via facsimile on November 8, 2005. The Applicant has indicated that this data is not readily available. As such, the proposed additions to the label for the interaction between EFV and indinavir/ritonavir have been rejected.

The applicant should provide further justification for the addition of pimozide and bepredil to Table 5 of the PI and the Patient Information Leaflet for SUSTIVA®. To date, there are no *in vivo* data that support the potential for efavirenz to inhibit CYP-3A4 substrates.

The applicant should revise the SUSTIVA® label to list the St. John's wort information in Table 5 (Should not coadminister) and remove it from Table 6 (Established or potential interactions).

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

There are two full drug interaction studies included in the Applicant's submission, that of EFV with carbamazepine and EFV with three HMG-CoA reductase inhibitors. Both of these studies were conducted by the Applicant. In addition, C_{min} data from 8 previously submitted PK studies conducted by the Applicant are analyzed and reported in the submission. The following is a summary of the important Clinical Pharmacology findings from these studies. Study design and results are discussed in more detail in Sections 3.1 – 3.3.

1.3.1. Carbamazepine

An open-label, sequential-design study was conducted in healthy volunteers in two cohorts to evaluate the effect of carbamazepine (CBZ) on the steady-state PK of EFV, and the effect of EFV on the steady-state PK of CBZ. Both drugs were administered in the fasted state. (See section 3.1 for full study methods.) The results of this study demonstrate a 2-way interaction in which both CBZ and EFV exposures are significantly decreased. The geometric mean values of CBZ AUC_{τ}, C_{max} and C_{min} were 27%, 20% and 35% lower, respectively, following co-administration with EFV. These values for EFV were 33%, 17%, and 43% lower, respectively, in the presence of CBZ. (See Tables 1.3.1.1 and 1.3.1.2.)

Table 1.3.1.1. Statistical Analyses of EFV PK parameter values at steady-state (n = 15)

Pharmacokinetic Parameter	Adjusted Geometric Means		Ratios of Adj. Geo. Means Pt. Estimate (90% CI) (Day 35 vs. Day 14)
	Efavirenz Alone (Day 14)	Efavirenz with Carbamazepine (Day 35)	
AUC(TAU) (µg•h/mL)	76.24	51.44	0.675 (0.602, 0.756)
Cmax (µg/mL)	5.84	4.84	0.827 (0.749, 0.914)
Cmin (µg/mL)[a]	2.17	1.24	0.569 (0.479, 0.677)

[a] 24 hour post dose
Day 14: 600 mg Efavirenz QD in Cohort 1
Day 35: 600 mg Efavirenz QD + 400 mg Carbamazepine QD in Cohort 1

Table 1.3.1.2. Statistical Analyses of CBZ PK parameter values at steady-state (n = 12)

Pharmacokinetic Parameter	Adjusted Geometric Means		Ratios of Adj. Geo. Means Pt. Estimate (90% CI) (Day 35 vs. Day 21)
	Carbamazepine Alone (Day 21)	Carbamazepine with Efavirenz (Day 35)	
AUC(TAU) (µg•h/mL)	138.89	101.31	0.729 (0.668, 0.796)
Cmax (µg/mL)	7.89	6.34	0.804 (0.761, 0.849)
Cmin (µg/mL)[a]	4.06	2.65	0.652 (0.560, 0.760)

[a] 24 hour post dose
Day 21: 400 mg Carbamazepine QD in Cohort 2
Day 35: 400 mg Carbamazepine QD + 600 mg Efavirenz QD in Cohort 2

All of the subjects administered EFV alone had C_{min} values > 1 µg/mL, compared with 53% of patients following co-administration with CBZ. Results of this PK study suggest a dose increase in EFV may be indicated during administration with CBZ, although a regimen cannot be recommended at this time without supporting data. As such, the combination should be avoided if possible.

The recommended range for therapeutic plasma concentrations of CBZ is between 4 and 12 µg/mL. When CBZ was administered alone in Cohort 2, 100% of Css,av values were > 4 µg/mL, compared to 67% of Css,av values during co-administration with EFV (Cohorts 1 and 2). Close therapeutic monitoring of CBZ concentrations is recommended during initiation or discontinuation of EFV therapy.

1.3.2. HMG-CoA Reductase Inhibitors

An open-label drug interaction study was conducted in 52 healthy adult subjects to evaluate the effect of EFV administration on the PK of simvastatin (SIM), atorvastatin (ATV), and pravastatin (PRA), as well as the effect of each HMG-CoA reductase inhibitor on the PK of EFV at steady-state. The 3 treatment arms consisted of: Arm A (N=19) – 40 mg QD SIM; Arm B (N=18) – 10 mg ATR; Arm C (N=15) – 40 mg PRA. The HMG-CoA reductase inhibitors were administered in the evening with a meal on Days 0 – 3, followed by determination of 24-hour PK on Day 3. On Days 5 – 14, EFV was administered alone at bedtime. On Days 15 – 18, EFV was co-administered with the HMG-CoA reductase inhibitors in the evening, with the final PK determination performed on Day 18. EFV was administered with a light meal on days in which PK measurements were made.

Plasma concentrations of each HMG-CoA reductase inhibitor, as well as the major active metabolites, were compared between Days 18 and 3. As simvastatin and simvastatin acid are believed to account for only a portion of the drug's activity, quantification of systemically available HMG-CoA reductase inhibitors in plasma was determined using an enzyme inhibition assay (EIA).

Table 1.3.2.1. Statistical Analysis of PK Parameters for Simvastatin, Atorvastatin and Pravastatin With and Without EFV. (90% CIs for the geometric mean ratios)

PK Parameter	Simvastatin N = 14	Simvastatin Acid N = 14	Active HMG-CoA Reductase Inhibitors N = 14	Total HMG-CoA Reductase Inhibitors N = 14
AUC 90% CI	0.27 – 0.38	0.32 – 0.61	0.32 – 0.48	0.26 – 0.46
C_{max} 90% CI	0.21 – 0.37	0.42 – 0.68	0.22 – 0.45	0.15 – 0.42
	Atorvastatin N = 14	**2-Hydroxy Atorvastatin** N = 14	**4-Hydroxy Atorvastatin** N = 14	**Total Active Atorvastatin** N = 14
AUC 90% CI	0.50 – 0.66	0.60 – 0.87	0.69 – 1.00	0.59 – 0.79
Cmax 90% CI	0.74 – 0.99	0.77 – 1.04	0.49 – 0.91	0.74 – 0.98
	Pravastatin N = 14			
AUC 90% CI	0.43 – 0.74			
Cmax 90% CI	0.41 – 1.12			

Note- GMR point estimates were not included in the report.
Cmin data were not included in the report.

Co-administration of EFV with SIM significantly reduced the systemic exposure of SIM, as assessed by AUC and C_{max} (median decreases 69% and 76%, respectively). Further, significant decreases in simvastatin acid and active and total HMG Co-A reductase

inhibitor exposure were also observed. ATV exposure, as well as that of the 2- and 4-hydroxymetabolites, was also significantly reduced. Total active ATV exposure was decreased by a median of 34.5%. EFV reduced PRA AUC and C_{max} values by a median of 40% and 18%, respectively.

EFV exposure was not significantly different following co-administration with the HMG-CoA reductase inhibitors; as such, no dosage adjustment of EFV is necessary. It is recommended that management of the interaction resulting in decreased SIM, ATV, and PRA exposure be managed by careful titration of their respective doses to obtain the desired clinical effect.

1.3.3. C_{min} results of EFV and co-administered drugs

The objective of this part of the Applicant's submission was to provide C_{min} values for EFV and co-administered drugs from previously reported studies that are missing from the package insert (lamivudine, zidovudine, fluconazole, clarithromycin, ethinyl estradiol, azithromycin, nelfinavir, rifampin and cetirizine). The missing C_{min} values were extracted from eight previously reported clinical study reports. Please refer to the following original study reports for study design details: AI66004, AI66015, AI66016, AI66017, AI66018, AI66019, AI66029, AI66102.

The C_{min} values of EFV and the co-administered drugs reported in the review are generally consistent with the previously reported AUC and C_{max} values of the same studies. See section 3.1.3. for the results.

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