SUSTIVA™
(efavirenz capsules)
Rx Only

SUSTIVA (efavirenz) in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection. This indication is based on analyses of plasma HIV-RNA levels and CD4 cell counts in controlled studies of up to 24 weeks in duration. At present, there are no results from controlled trials evaluating long-term suppression of HIV-RNA with SUSTIVA.

Resistant virus emerges rapidly when non-nucleoside reverse transcriptase inhibitors (NNRTIs) are administered as monotherapy. Therefore, SUSTIVA must not be used as a single agent to treat HIV or added on as a sole agent to a failing regimen. SUSTIVA therapy should always be initiated in combination with at least one other antiretroviral agent to which the patient has not been previously exposed.

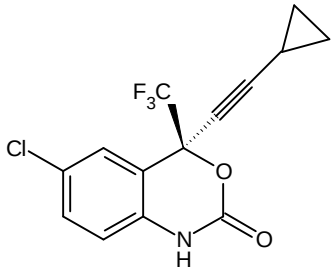
DESCRIPTION

SUSTIVA (efavirenz**)** is an HIV-1 specific, non-nucleoside, reverse transcriptase inhibitor (NNRTI).

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.

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 is a non-nucleoside reverse transcriptase (RT) inhibitor of human immunodeficiency virus type 1 (HIV-1). Efavirenz activity is mediated predominantly by non-competitive inhibition of HIV-1 RT. HIV-2 RT and human cellular DNA polymerases alpha, beta, gamma, and delta are not inhibited by efavirenz.

***In vitro* HIV Susceptibility:** The clinical significance of *in vitro* susceptibility of HIV-1 to efavirenz has not been established. The *in vitro* antiviral activity of efavirenz was assessed in lymphoblastoid cell lines, peripheral blood mononuclear cells (PBMCs) and macrophage/monocyte cultures. The 90-95% inhibitory concentration (IC_{90-95}) of efavirenz for wild type laboratory adapted strains and clinical isolates ranged

from 1.7 to 25 nM. Efavirenz demonstrated synergistic activity against HIV-1 in cell culture when combined with zidovudine (ZDV), didanosine, or indinavir (IDV).

Resistance: HIV-1 isolates with reduced susceptibility to efavirenz (>380-fold increase in IC_{90}) compared to baseline can emerge *in vitro*. Phenotypic (N=26) changes in evaluable HIV-1 isolates and genotypic (N=62) changes in plasma virus from selected patients treated with efavirenz in combination with IDV, or with ZDV plus lamivudine were monitored. One or more RT mutations at amino acid positions 100, 101, 103, 108, 190 and 225, were observed in all 62 patients with a frequency of at least 10% compared to baseline. The mutation at RT amino acid position 103 (lysine to asparagine) was the most frequently observed (≥90%). A mean loss in susceptibility (IC_{90}) to efavirenz of 47-fold was observed in 26 clinical isolates. Five clinical isolates were evaluated for both genotypic and phenotypic changes from baseline. Decreases in efavirenz susceptibility (range from 9 to >312-fold increase in IC_{90}) were observed for these isolates *in vitro* compared to baseline. All 5 isolates possessed at least one of the efavirenz-associated RT mutations. The clinical relevance of phenotypic and genotypic changes associated with efarivenz therapy has not been established.

Cross-Resistance: Rapid emergence of HIV-1 strains that are cross-resistant to non-nucleoside RT inhibitors has been observed *in vitro*. Thirteen clinical isolates previously characterized as efavirenz-resistant were also phenotypically resistant to nevirapine and delavirdine *in vitro* compared to baseline. Clinically derived ZDV-resistant HIV-1 isolates tested *in vitro* retained susceptibility to efavirenz. Cross-resistance between efavirenz and HIV protease inhibitors is unlikely because of the different enzyme targets involved.

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 QD, steady-state C_{max} was 12.9 ± 3.7 μM (mean ± S.D.), steady-state C_{min} was 5.6 ± 3.2 μM, and AUC was 184 ±73 μM•h.

Effect of Food on Oral Absorption: In uninfected volunteers, meals of normal composition had no appreciable effect on the bioavailability of 100 mg of an investigational efavirenz formulation administered twice a day for 10 days with meals (Breakfast: 662 kcal, 13.8 g protein, 27.9 g fat, 94.6 g carbohydrate; Dinner: 567 kcal, 44.5 g protein, 12.5 g fat, 73.8 g carbohydrate). The relative bioavailability of a single 1200 mg dose of an investigational efavirenz formulation in uninfected volunteers (N=5) was increased 50% (range 11%-126%) following a high fat meal (1070 kcal, 82 g fat, 69% of calories from fat) (see **DOSAGE AND ADMINISTRATON**).

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 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 Ki 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 (Ki values 82-160 µM) only at concentrations well above those achieved clinically. The effects on CYP3A4 activity are expected to be similar between 200 mg, 400 mg and 600 mg doses of efavirenz. Coadministration of efavirenz with drugs primarily metabolized by 2C9, 2C19 and 3A4 isozymes may result in altered plasma concentrations of the coadministered drug. Drugs which induce CYP3A4 activity would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations.

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

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

Coadministered Drug:	Dose	Efavirenz Dose	Number of Subjects	Coadministered Drug (% change) C_{max} (mean [90% CI])	Coadministered Drug (% change) AUC (mean [90% CI])
Indinavir	800 mg q8h x 14 days	200 mg x 14 days	17	⇓ (16%) [-10-35%]	⇓ (31%) [13-45%]
Nelfinavir Metabolite AG-1402	750 mg q8h x 7 days	600 mg x 7 days	10	⇑ (21%) [10-33%] ⇓ (40%) [30-48%]	⇑ (20%) [8-34%] ⇓ (37%) [25-48%]
Ritonavir	500 mg q12h x 8 days After AM dose After PM dose	600 mg x 10 days	11	⇑(24%) [12-38%] ⇔	⇑ (18%) [6-33%] ⇔
Saquinavir SGC*	1200 mg q8h x 10 days	600 mg x 10 days	12	⇓(50%) [28-66%]	⇓ (62%) [45-74%]
Lamivudine	150 mg q12h x 14 days	600 mg x 14 days	9	⇔	⇔
Zidovudine	300 mg q12h x 14 days	600 mg x 14 days	9	⇔	⇔
Azithromycin	600 mg single dose	400 mg x 7 days	14	⇑ (22%) [4-42%]	⇔
Clarithromycin 14-OH metabolite	500 mg q12h x 7 days	400 mg x 7 days	11	⇓ (26%) [15-35%] ⇑ (49%) [32-69%]	⇓ (39%) [30-46%] ⇑ (34%) [18-53%]
Fluconazole	200 mg x 7 days	400 mg x 7 days	10	⇔	⇔
Ethinyl Estradiol	50 µg single dose	400 mg x 10 days	13	⇔	⇑ (37%) [25-51%]

⇑ Indicates increase ⇓ Indicates decrease ⇔ Indicates no change

* Soft Gelatin Capsule

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

Coadministered Drug:	Dose	Efavirenz Dose	Number of Subjects	Efavirenz (% change) C_{max} (mean [90% CI])	Efavirenz (% change) AUC (mean [90% CI])
Indinavir	800 mg q8h x 14 days	200 mg x 14 days	11	⇔	⇔
Nelfinavir	750 mg q8h x 7 days	600 mg x 7 days	10	⇔	⇔
Ritonavir	500 mg q12h x 8 days	600 mg x 10 days	9	⇑ (14%) [4-26%]	⇑ (21%) [10-34%]
Saquinavir SGC*	1200 mg q8h x 10 days	600 mg x 10 days	13	⇓ (13%) [5-20%]	⇓ (12%) [4-19%]
Rifampin	600 mg x 7 days	600 mg x 7 days	12	⇓ (20%) [11-28%]	⇓ (26%) [15-36%]
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%]
Famotidine	40 mg single dose	400 mg single dose	17	⇔	⇔
Mylanta DS**	30 mL single dose	400 mg single dose	17	⇔	⇔
Ethinyl Estradiol	50 µg single dose	400 mg x 10 days	13	⇔	⇔

⇑ Indicates increase ⇓ Indicates decrease ⇔ Indicates no change
* Soft Gelatin Capsule
** Contains aluminum hydroxide 400 mg, magnesium hydroxide 400 mg, plus simethicone 40 mg

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 analyses of plasma HIV-RNA levels and CD4 cell counts in controlled studies of up to 24 weeks in duration. At present, there are no results from controlled trials evaluating long-term suppression of HIV-RNA with SUSTIVA.

Description of Studies

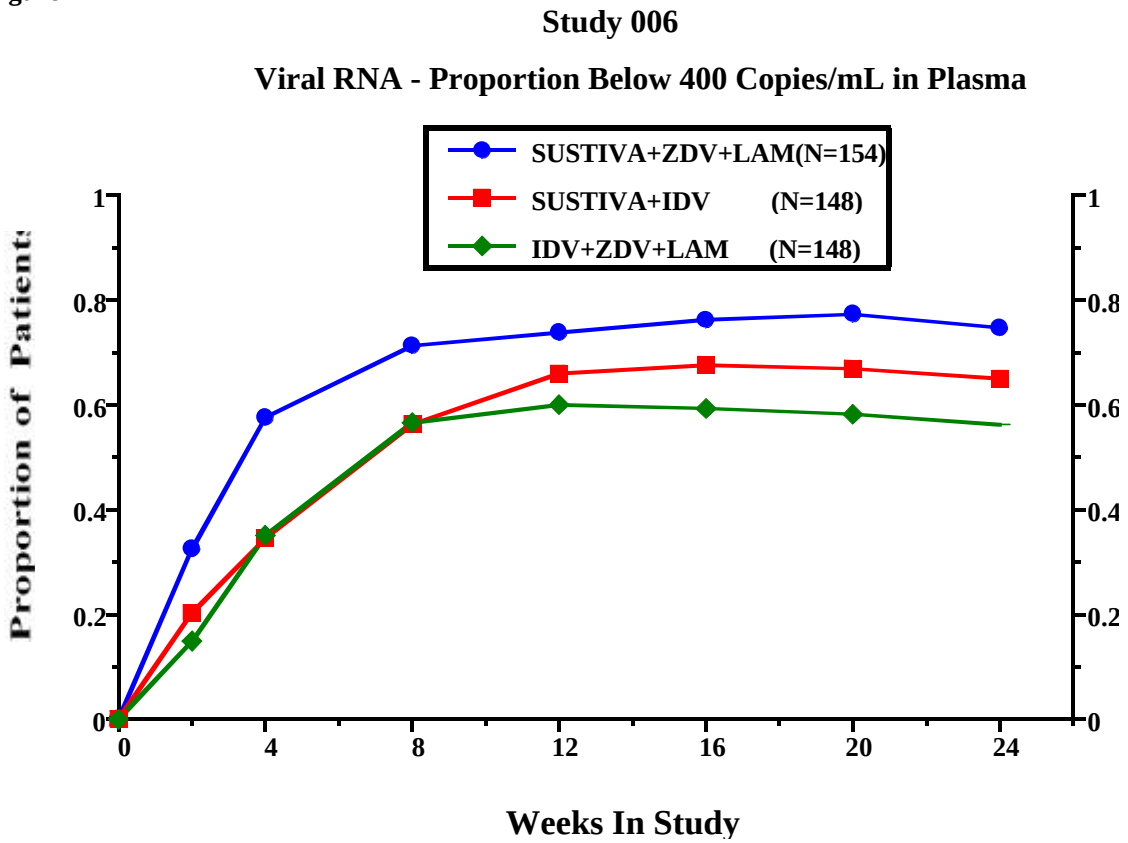
In the clinical studies described below, the primary efficacy measure was the percent of patients with plasma HIV-RNA <400 copies/mL (<500 copies/mL in ACTG 364), using the Roche RT-PCR (Amplicor™) HIV-1 Monitor assay.

In the analysis presented in each figure, patients who terminated the study early for any reason or who had a missing HIV-RNA measurement that was either preceded or followed by a measurement above the limit of assay quantification were considered to have HIV-RNA above 400 copies/mL at the missing time points.

Study 006 is an ongoing, randomized, open-label trial to evaluate the plasma HIV-RNA suppression achieved by the combination of SUSTIVA (600 mg QD) + indinavir (IDV, 1000 mg q8h) or SUSTIVA

(600 mg QD) + zidovudine (ZDV, 300 mg q12h) + lamivudine (LAM, 150 mg q12h) versus indinavir (800 mg q8h) + zidovudine (300 mg q12h) + lamivudine (150 mg q12h). Twenty-four week data analyses are presented for 450 patients (mean age 36.3 years [range 18-64], 60% Caucasian, 86% male). Overall mean baseline CD4 count was 345 cells/mm^3, and mean HIV-RNA plasma level was 4.77 log_{10} copies/mL. The percent of patients achieving plasma HIV-RNA levels <400 copies/mL is presented in Figure 1. Through 24 weeks of therapy, there was no significant difference in the mean CD4 cell count between the treatment arms; the overall mean increase was 143 cells.

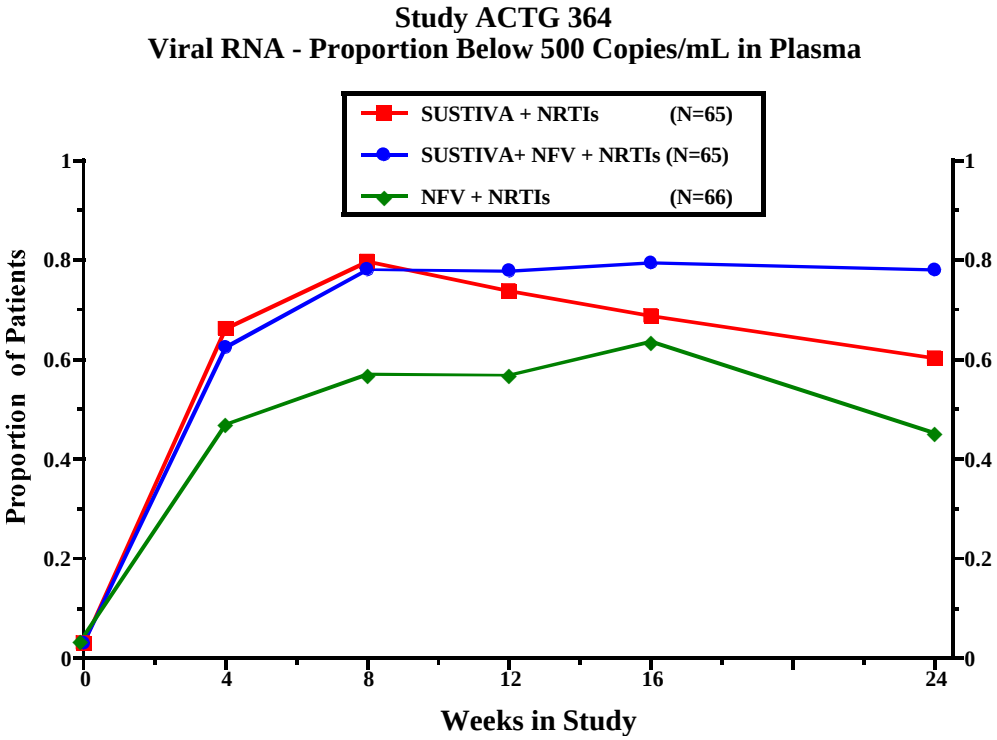
Figure 1



More subjects on the IDV+ZDV+LAM control arm (56 subjects) discontinued the study prior to 24 weeks compared to either the SUSTIVA (efavirenz) +ZDV+LAM arm (32 subjects) or the SUSTIVA+IDV arm (35 subjects). These differences in discontinuation rates were predominantly the result of adverse events in the IDV+ZDV+LAM control arm. Subjects discontinuing from the study before 24 weeks were counted as HIV-RNA ≥400 copies/mL. Therefore, differences in discontinuations as a result of adverse events among the regimens accounted for a substantial fraction of the difference in the percent below 400 copies/mL. It is difficult to assess the relative efficacy of the treatment arms given the disproportional discontinuations in an open label study.

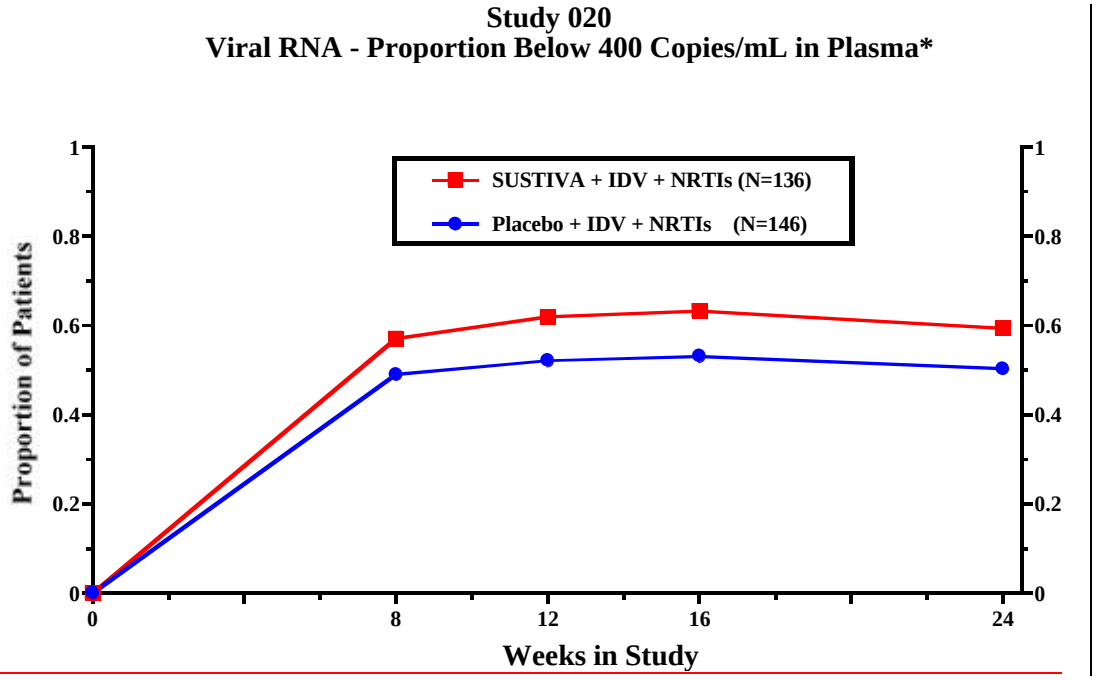
ACTG 364 is an ongoing 48-week double-blind, placebo-controlled study in NRTI-experienced patients who had completed two prior ACTG studies. The initial protocol-defined analysis was based on results after 16 weeks of therapy. One-hundred and ninety-six HIV-infected patients (mean age 41 years [range 18-76], 74% Caucasian, 88% male) received NRTIs in combination with SUSTIVA (600 mg QD), or nelfinavir (NFV, 750 mg TID), or SUSTIVA (600 mg QD) + nelfinavir in a randomized double-blinded manner. Upon entry into the study, all patients were assigned a new open label NRTI regimen, which was dependent on their previous NRTI treatment experience. The percent of patients achieving plasma HIV-RNA levels <500 copies/mL at the time of a preliminary non-protocol specified analysis at 24 weeks is presented in Figure 2. Through 24 weeks of therapy, there was no significant difference in the mean CD4 cell count between the treatment arms; the overall mean increase was 65 cells.

Figure 2



Study 020 is an ongoing, randomized, double-blind, placebo-controlled 24-week study in NRTI-experienced, protease inhibitor and NNRTI-naive patients designed to compare therapy consisting of SUSTIVA + indinavir + nucleoside analogue reverse transcriptase inhibitors versus therapy consisting of indinavir + NRTIs at 24 weeks of treatment. Patients were randomized to receive either SUSTIVA (600 mg QD) + indinavir (1000 mg q8h) + NRTIs or indinavir (800 mg q8h) + NRTIs. Sixty-eight percent of the 282 patients (mean age 38.9 years [range 22-69], 53% Caucasian, 83% male) changed their NRTI regimen at study initiation. Mean baseline CD4 count was 330 cells/mm^3, and mean HIV-RNA plasma level was 4.39 $\log_{10}$ copies/mL. Data on 282/330 patients who completed 24 weeks of treatment and achieved plasma HIV-RNA levels <400 copies/mL is presented in Figure 3. Through 24 weeks of therapy, there was no significant difference in the mean CD4 cell count between the treatment arms; the overall mean increase was 110 cells.

Figure 3



***There was no significant difference between the two treatment arms in the percent of patients achieving plasma HIV-RNA levels <400 copies/mL at 24 weeks.**

CONTRAINDICATIONS

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

WARNINGS

Resistant virus emerges rapidly when NNRTIs are administered as monotherapy. Therefore, SUSTIVA must not be used as a single agent to treat HIV or added on as a sole agent to a failing regimen. SUSTIVA therapy should always be initiated in combination with at least one other new antiretroviral agent to which the patient has not been previously exposed.

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

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 (e.g., cardiac arrhythmias, prolonged sedation or respiratory depression).

PRECAUTIONS

General

Nervous System Symptoms: There have been reports (approximately 1-2 per thousand SUSTIVA-treated patients) of delusions and inappropriate behavior, predominantly in patients with a history of mental illness or substance abuse. Severe acute depression (including suicidal ideation/attempts) has also been infrequently reported in both SUSTIVA-treated and control-treated patients. Patients who experience these symptoms should contact their doctor immediately because discontinuation of SUSTIVA may be required.

Fifty-two percent of patients receiving SUSTIVA reported central nervous system and psychiatric symptoms. These symptoms included, but were not limited to, dizziness, impaired concentration, somnolence, abnormal dreams and insomnia. In controlled trials, these symptoms were severe in 2.6% of patients receiving SUSTIVA 600 mg QD and in 1.4% of patients receiving control regimens. In clinical trials, 2.6% of SUSTIVA-treated patients discontinued therapy because of nervous system symptoms. These symptoms usually begin during the first or second day of therapy and generally resolve after the first 2-4 weeks. Patients should be informed that these symptoms are likely to improve with continued therapy. Dosing at bedtime improves the tolerability of these symptoms and is recommended during the first weeks of therapy and in patients who continue to experience these symptoms (see **ADVERSE REACTIONS**).

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 should be informed that SUSTIVA may cause dizziness, impaired concentration, and/or drowsiness. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery.

Skin Rash: In controlled clinical trials, 27% (124/455) of patients treated with 600 mg SUSTIVA experienced new onset skin rash compared with 17% (61/351) of patients treated in control groups. Rash associated with blistering, moist desquamation, or ulceration occurred in 1% (3/455) of patients treated with SUSTIVA. In all studies and expanded access, one adult developed erythema multiforme and another Stevens-Johnson Syndrome among approximately 2200 treated patients. The median time to onset of rash in adults was 11 days and the median duration, 14 days. The discontinuation rate for rash in clinical trials was 1.7% (8/455). 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 23 of 57 pediatric patients (40%) treated with SUSTIVA. Two pediatric patients experienced Grade 3 rash (one confluent rash with fever; one urticaria), and two patients had Grade 4 rash (erythema multiforme). The median time to onset of rash in children was eight days. Prophylaxis with appropriate antihistamines prior to initiating therapy with SUSTIVA in children 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 5 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.

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

Information for Patients

Patients should be informed that SUSTIVA is not a cure for HIV infection and that they may continue to develop opportunistic infections and other complications associated with HIV disease. The long-term effects of SUSTIVA (efavirenz) are unknown at this time. 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 not alter the dose or discontinue therapy without consulting their physician.

Patients should be informed that central nervous system symptoms occur in approximately half the patients taking SUSTIVA and that SUSTIVA may cause dizziness, impaired concentration, delusions, depression and/or drowsiness. These symptoms are likely to improve with continued therapy. Dosing at bedtime improves the tolerability of these symptoms and is recommended during the first weeks of therapy and in patients who continue to experience these symptoms. 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 should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery.

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

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

SUSTIVA may interact with some drugs; therefore, patients should be advised to report the use of any prescription or non-prescription medication to their physician.

High fat meals may increase the absorption of SUSTIVA and should be avoided. SUSTIVA may be taken with meals of normal fat content (see **CLINICAL PHARMACOLOGY; Effect of Food on Oral Absorption**).

Drug Interactions (see also 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 (e.g., phenobarbital, rifampin, rifabutin) would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations. Drug interactions with SUSTIVA are summarized in Table 3.

Table 3*

Drugs That Should Not Be Coadministered With SUSTIVA

Drug Class	Drugs Within Class Not To Be Coadministered With SUSTIVA
Antihistamines	astemizole

Benzodiazepines	midazolam, triazolam
GI Motility Agents	cisapride
Anti-Migraine	ergot derivatives

Drugs That Require A Dose Adjustment When Coadministered With SUSTIVA

Drug Class	Drug Within Class Requiring Dose Increase
Anti-HIV Protease Inhibitor	indinavir (increase dose from 800 mg to 1000 mg every 8 hours)

Other Potentially Clinically Significant Drug Interactions With SUSTIVA

Anticoagulants: Warfarin	Plasma concentrations and effects potentially increased or decreased by SUSTIVA
Anti-HIV Protease Inhibitor: Saquinavir	Plasma concentrations decreased by SUSTIVA; should not be used as sole protease inhibitor in combination with SUSTIVA
Antimycobacterial Agents	
Clarithromycin	Plasma concentrations decreased by SUSTIVA; clinical significance unknown
Rifabutin	Effects unknown
Rifampin	Decreases efavirenz plasma concentrations; clinical significance unknown
Estrogens: Ethinyl Estradiol	Plasma concentrations increased by SUSTIVA; clinical significance unknown

* See Tables 1 and 2.

Concomitant Antiretroviral Agents:

Nelfinavir: The AUC and C_{max} of nelfinavir (750 mg q8h) are increased by 20% and 21%, respectively when given with SUSTIVA in uninfected volunteers. No dose adjustment is necessary when nelfinavir is administered in combination with SUSTIVA.

Indinavir: When indinavir (800 mg every 8 hours) was given with SUSTIVA, the indinavir AUC and C_{max} were decreased by approximately 31% and 16%, respectively as a result of enzyme induction. Therefore, the dose of indinavir should be increased from 800 mg to 1000 mg every 8 hours when SUSTIVA and indinavir are coadministered. No adjustment of the dose of SUSTIVA is necessary when given with indinavir.

Ritonavir: When SUSTIVA and ritonavir 500 mg (given every 12 hours) were studied in uninfected volunteers, the AUC for each drug was increased by approximately 20%. The combination was associated with a higher frequency of adverse clinical experiences (e.g., dizziness, nausea, paresthesia) and laboratory abnormalities (elevated liver enzymes). Monitoring of liver enzymes is recommended when SUSTIVA is used in combination with ritonavir.

Saquinavir: When saquinavir soft gelatin capsules (1200 mg q8h) were given with SUSTIVA to uninfected volunteers, saquinavir AUC and C_{max} were decreased by 62% and 50%, respectively. Use of SUSTIVA in combination with saquinavir as the sole protease inhibitor is not recommended.

Saquinavir/Ritonavir: No pharmacokinetic data are available on the potential interactions of SUSTIVA with the combination of saquinavir and ritonavir.

Nucleoside Analogue Reverse Transcriptase Inhibitors: Studies of the interaction between SUSTIVA and the combination of zidovudine (300 mg q12h) and lamivudine (150 mg q12h) were performed in HIV-infected patients. No clinically significant pharmacokinetic interactions were observed. Specific drug interaction studies have not been performed with SUSTIVA and other NRTIs. 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.

Non-Nucleoside Reverse Transcriptase Inhibitors: No studies have been performed with SUSTIVA in combination with other NNRTIs.

Antimicrobial Agents:

Rifamycins: Rifampin (600 mg daily) reduced efavirenz AUC by 26% and C_{max} by 20% in 12 uninfected volunteers. Adjustment of the dose of SUSTIVA when taken with rifampin is not recommended; however, the clinical significance of the reduced efavirenz levels is not known. No dose adjustment of rifampin is recommended when given with SUSTIVA. Rifabutin has not been studied in combination with SUSTIVA; however, there is a potential for an interaction.

Macrolide Antibiotics:

Azithromycin: Coadministration of single 600 mg doses of azithromycin and multiple doses of SUSTIVA in uninfected volunteers did not result in any clinically significant pharmacokinetic interaction. No dosage adjustment is necessary when azithromycin is given in combination with SUSTIVA.

Clarithromycin: Coadministration of SUSTIVA with clarithromycin given as 500 mg every 12 hours for seven days resulted in a significant effect of efavirenz on the pharmacokinetics of clarithromycin. The AUC and C_{max} of clarithromycin decreased 39% and 26%, respectively, while the AUC and C_{max} of the clarithromycin hydroxymetabolite were increased 34% and 49%, respectively, when used in combination with SUSTIVA. The clinical significance of these changes in clarithromycin plasma levels is not known. 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.

Other macrolide antibiotics, such as erythromycin, have not been studied in combination with SUSTIVA.

Antifungal Agents:

No clinically significant pharmacokinetic interactions were seen when fluconazole (200 mg daily) and SUSTIVA were coadministered to uninfected volunteers. No dosage adjustment is necessary when the two drugs are used in combination. The potential for drug interactions with SUSTIVA and other imidazole and triazole antifungals, such as itraconazole and ketoconazole, has not been studied.

Other Drug Interactions:

Antacids/famotidine: Neither aluminum/magnesium hydroxide antacids (30 mL single dose) nor famotidine (40 mg single dose) altered the absorption of efavirenz in uninfected volunteers. These data suggest that alteration of gastric pH by other drugs would not be expected to affect efavirenz absorption.

Oral Contraceptives (ethinyl estradiol): Only the ethinyl estradiol component of oral contraceptives has been studied in combination with SUSTIVA. The AUC following a single dose of 50 µg ethinyl estradiol was increased (37%) by efavirenz. No significant changes were observed in C_{max} of ethinyl estradiol. The clinical significance of these effects is not known. No effect of a single dose of ethinyl estradiol on efavirenz C_{max} or AUC was observed. Because the potential interaction of efavirenz with oral contraceptives has not been fully characterized, a reliable method of barrier contraception should be used in addition to oral contraceptives.

Carcinogenesis, Mutagenesis and Impairment of Fertility:
Long-term carcinogenicity studies of efavirenz in rats and mice are in progress.

Efavirenz was not mutagenic or genotoxic in *in vitro* and *in vivo* genotoxicity assays which included bacterial mutation assays in *S. typhimurium* and *E. coli*, mammalian mutation assays in Chinese Hamster Ovary cells, chromosomal aberration assays in human peripheral blood lymphocytes or Chinese Hamster Ovary cells, and an *in vivo* mouse bone marrow micronucleus assay.

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

Pregnancy:
Pregnancy Category C: 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 (post coital 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. Because teratogenic effects have been seen in primates at efavirenz exposures similar to those seen in the clinic at the recommended dose, pregnancy should be avoided in women receiving SUSTIVA. Barrier contraception should always be used in combination with other methods of contraception (e.g., oral or other hormonal contraceptives). Women of childbearing potential should undergo pregnancy testing prior to initiation of SUSTIVA **(**see **WARNINGS)**.

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 QD of SUSTIVA (efavirenz). 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 QD of SUSTIVA.

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.

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.

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 infection. Studies in rats have demonstrated that efavirenz is excreted in milk. Mothers should be instructed not to breast-feed if they are receiving SUSTIVA.

Pediatric Use:
ACTG 382 is an ongoing open-label 48-week 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. 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 40% (23/57) of pediatric patients compared to 28% of adults, and a higher frequency of Grade 3 or 4 rash reported in 7% (4/57) of pediatric patients compared to 0.7% of adults **(**see **ADVERSE REACTIONS; Table 5)**.

The starting dose of SUSTIVA was 600 mg QD 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 ± S.D.), 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 and over to determine whether they respond differently from younger subjects.

ADVERSE REACTIONS

SUSTIVA has been studied in 2215 patients. The most significant adverse events associated with SUSTIVA therapy are nervous system symptoms and rash.

Nervous System Symptoms: Fifty-two percent of patients receiving SUSTIVA reported central nervous system and psychiatric symptoms. Table 4 lists the frequency of symptoms of different degrees of severity, and gives the discontinuation rates, in clinical trials for the central nervous system symptom of dizziness or for one or more of the following psychiatric symptoms: somnolence, insomnia, abnormal dreaming, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations and euphoria. The frequencies of specific central and peripheral nervous system symptoms and psychiatric symptoms are provided in Table 6 (see **PRECAUTIONS; General**).

Table 4
Percent of Patients with One or More Selected Nervous System Symptoms[1,2]

Percent of Patients with:	SUSTIVA 600 mg QD (N=455)	Control Groups (N=351)
	%	%
Mild Symptoms[3]	31.4	16.5
Moderate Symptoms[4]	17.8	8.0
Severe Symptoms[5]	2.6	1.4
Symptoms of Any Severity	51.9	25.9
Treatment discontinuation as a result of symptoms	2.6	0.6

1. Includes events reported regardless of causality.
2. Data from Studies 006, 020, and two Phase 2 studies.
3. "Mild" = Symptoms which do not interfere with patient's daily activities.
4. "Moderate" = Symptoms which may interfere with daily activities.
5. "Severe" = events which interrupt patient's usual daily activities.

Skin Rash: Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first two 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 is recommended 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 5.

Table 5
Percent of Patients with Treatment-Emergent Rash[1,2]

Percent of Patients with:	Description of Rash Grade[3]	SUSTIVA 600 mg QD Adults (N=455)	SUSTIVA Children (N=57)	Control Groups Adults (N=351)
		%	%	%
Grade 1 Rash	Erythema, pruritus	9.9	8.8	9.4
Grade 2 Rash	Diffuse maculopapular rash, dry desquamation	16.7	24.5	8.0
Grade 3 Rash	Vesiculation, moist desquamation, ulceration	0.7	3.5	0.0
Grade 4 Rash	Erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis, necrosis requiring surgery, exfoliative dermatitis	0.0	3.5	0.0
Rash of Any Grade	-	27.3	40.3	17.3
Treatment discontinuation as a result of rash	-	1.7	8.8	0.3

1. Includes events reported regardless of causality.
2. Data from Studies 006, 020, and two Phase 2 studies.
3. NCI Grading System.

As seen in Table 5, rash is more common in children and more often of higher grade (i.e., more severe) **(**see **PRECAUTIONS; General**).

Experience with SUSTIVA 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.

Drug-related clinical adverse experiences of moderate or severe intensity observed in ≥2% of patients in three controlled clinical trials are presented in Table 6.

Table 6
Percent of Patients with Treatment-Emergent[1] Adverse Events of Moderate or Severe Intensity Reported in ≥2% of Patients in Studies 006, ACTG 364, and 020

Adverse Events	Study 006 LAM, NNRTI and Protease Inhibitor Naive Patients			Study ACTG 364 NRTI-experienced NNRTI and Protease Inhibitor Naive Patients			Study 020 NRTI-experienced NNRTI and Protease Inhibitor Naive Patients	
	SUSTIVA[2] + ZDV/LAM (N=148)	SUSTIVA[2] + Indinavir (N=141)	Indinavir + ZDV/LAM (N=142)	SUSTIVA[2] + Nelfinavir + NRTIs (N=64)	SUSTIVA[2] + NRTIs (N=65)	Nelfinavir + NRTIs (N=66)	SUSTIVA[2] + Indinavir + NRTIs (N=134)	Indinavir + NRTIs (N=144)
	%	%	%	%	%	%	%	%
Body as a Whole								
Fatigue	7	6	10	0	2	3	5	1
Central and Peripheral Nervous System								
Dizziness	10	6	1	2	5	0	8	1
Headache	6	6	5	5	0	2	6	4
Hypoesthesia	1	1	0	2	2	0	1	1
Gastrointestinal								
Nausea	12	6	25	0	2	0	11	10
Vomiting	7	3	16	--	--	--	6	6
Diarrhea	5	8	8	11	2	5	12	3
Dyspepsia	1	4	6	0	0	2	3	1
Abdominal Pain	1	1	4	0	0	2	3	1
Flatulence	1	1	2	0	0	0	0	1
Psychiatric								
Concentration Impaired	9	1	1	0	0	0	4	1
Insomnia	7	6	3	0	0	2	1	1
Abnormal Dreams	4	0	0	--	--	--	2	1
Somnolence	3	2	4	0	0	0	2	2
Depression	2	3	0	0	0	3	2	0
Anorexia	2	0	1	0	2	0	5	1
Nervousness	2	2	0	0	0	0	1	0
Skin & Appendages								
Rash	11	20	6	8	5	11	10	7
Pruritus	1	0	1	0	2	5	2	1
Increased Sweating	2	1	1	0	0	0	1	0
Urinary System Disorders								
Renal Calculus	0	1	4	0	0	0	1	3
Hematuria	1	0	4	--	--	--	0	1

1. Includes adverse events at least possibly related to study drug or of unknown relationship for Studies 006 and 020. Includes all adverse events regardless of relationship to study drug for Study ACTG 364.

2. SUSTIVA provided as 600 mg QD.

-- = Not Specified.

Clinical adverse experiences of moderate to severe intensity observed in ≥ 10% of 57 pediatric patients aged 3 to 16 years who received SUSTIVA (efavirenz), nelfinavir, and one or more NRTIs were: rash (40%), diarrhea/loose stools (39%), fever (26%), cough (25%), and nausea/vomiting (16%). The incidence of nervous system symptoms was 9% (5/57). Two patients experienced Grade 3 rash, two patients had Grade 4 rash, and five patients (9%) discontinued because of rash **(**see also **PRECAUTIONS; Pediatric Use**).

Adverse clinical experiences of moderate to severe intensity observed in less than 2% of patients receiving SUSTIVA in all Phase II/III studies, including the North American expanded access program, and considered at least possibly related or of unknown relationship to treatment and of at least moderate severity are listed below by body system:

Body as a Whole: alcohol intolerance, allergic reaction, asthenia, fever, hot flushes, malaise, pain, peripheral edema, syncope

Central and Peripheral Nervous System: ataxia, confusion, convulsions, impaired coordination, migraine headaches, neuralgia, paresthesia, peripheral neuropathy, speech disorder, tremor, vertigo

Gastrointestinal: dry mouth, pancreatitis

Hearing and Vestibular: tinnitus

Cardiovascular: flushing, palpitations, tachycardia, thrombophlebitis

Liver and Biliary System: hepatitis

Musculoskeletal: arthralgia, myalgia

Psychiatric: aggravated depression, agitation, amnesia, anxiety, apathy, emotional lability, euphoria, hallucination, psychosis

Respiratory: asthma

Skin and Appendages: alopecia, eczema, folliculitis, skin exfoliation, urticaria

Special Senses: abnormal vision, diplopia, parosmia, taste perversion

Laboratory Abnormalities:

Liver Enzymes: Among 393 patients treated with 600 mg of SUSTIVA in controlled clinical trials, 2% developed AST levels and 3% developed ALT levels greater than five times the upper limit of normal. Among 250 patients treated with control regimens, similar elevations of AST or ALT were seen in 3% and 2%, respectively.

Liver function tests should be monitored in patients with a prior history of Hepatitis B and/or C. In 53 patients treated with 600 mg of SUSTIVA who were seropositive for Hepatitis B and/or C, 6% developed AST levels and 13% developed ALT levels greater than five times the upper limit of normal. In 41 patients seropositive for Hepatitis B and/or C treated with control regimens, 5% developed AST elevations and 2% developed ALT elevations to these levels. Elevations of GGT to greater than five times the upper limit of the normal range were observed in 4% of all patients treated with 600 mg of SUSTIVA and in 11% of patients seropositive for Hepatitis B or C. In patients treated with control regimens, the incidence of GGT elevations to this level was 2%, irrespective of Hepatitis B or C serology. Isolated elevations of GGT in patients receiving SUSTIVA may reflect enzyme induction not associated with liver toxicity **(**see **PRECAUTIONS; General**).

Lipids: Increases in total cholesterol of 10-20% have been observed in some uninfected volunteers receiving SUSTIVA. Modest elevations of serum triglycerides and cholesterol have also been observed in non-fasting patients receiving SUSTIVA, however, the significance of these findings is unknown. The effect of SUSTIVA on total, LDL, and HDL cholesterol in patients receiving therapy with SUSTIVA has not been well-characterized (see **PRECAUTIONS; General**).

Cannabinoid Test Interaction: Efavirenz does not bind to cannabinoid receptors. False positive urine cannabinoid test results have been reported in uninfected volunteers who received SUSTIVA. False positive test results have only been observed with the CEDIA DAU Multi-Level THC assay, which is used for screening, and have not been observed with other cannabinoid assays tested including tests used for confirmation of positive results.

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 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). SUSTIVA may be taken with or without food; however, a high fat meal may increase the absorption of SUSTIVA and should be avoided (see **CLINICAL PHARMACOLOGY; Effect of Food on Oral Absorption**).

In order to improve the tolerability of nervous system side effects, bedtime dosing is recommended during the first two to four weeks of therapy and in patients who continue to experience these symptoms **(**see **PRECAUTIONS; General** 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: Table 7 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 7
Pediatric Dose to be Administered Once Daily

Body Weight		**SUSTIVA**
Kg	Lbs	**Dose (mg)**
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

SUSTIVA capsules are available as follows:

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

Bottles of 90 NDC 0056-0474-92

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

Bottles of 30 NDC 0056-0473-30

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

Bottles of 30 NDC 0056-0470-30

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

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6495-00/September, 1998