SUSTIVA™
(efavirenz) capsules
Rx only

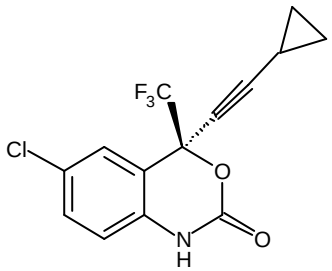
DESCRIPTION

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=104) 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 98, 100, 101, 103, 106, 108, 188, 190 and 225, were observed in 102 of 104

patients with a frequency of at least 9% 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 efavirenz therapy is under evaluation.

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 once daily, 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 ADMINISTRATION**).

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 efavirenzelimination 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 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	750 mg q8h x 7 days	600 mg x 7 days	10	⇑ (21%) [10-33%]	⇑ (20%) [8-34%]
Metabolite AG-1402				⇓ (40%) [30-48%]	⇓ (37%) [25-48%]
Ritonavir	500 mg q12h x 8 days 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	500 mg q12h x 7 days	400 mg x 7 days	11	⇓ (26%) [15-35%]	⇓ (39%) [30-46%]
14-OH metabolite				⇑ (49%) [32-69%]	⇑ (34%) [18-53%]
Fluconazole	200 mg x 7 days	400 mg x 7 days	10	⇔	⇔
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 two clinical trials of at least one year duration that demonstrated prolonged suppression of HIV-RNA.

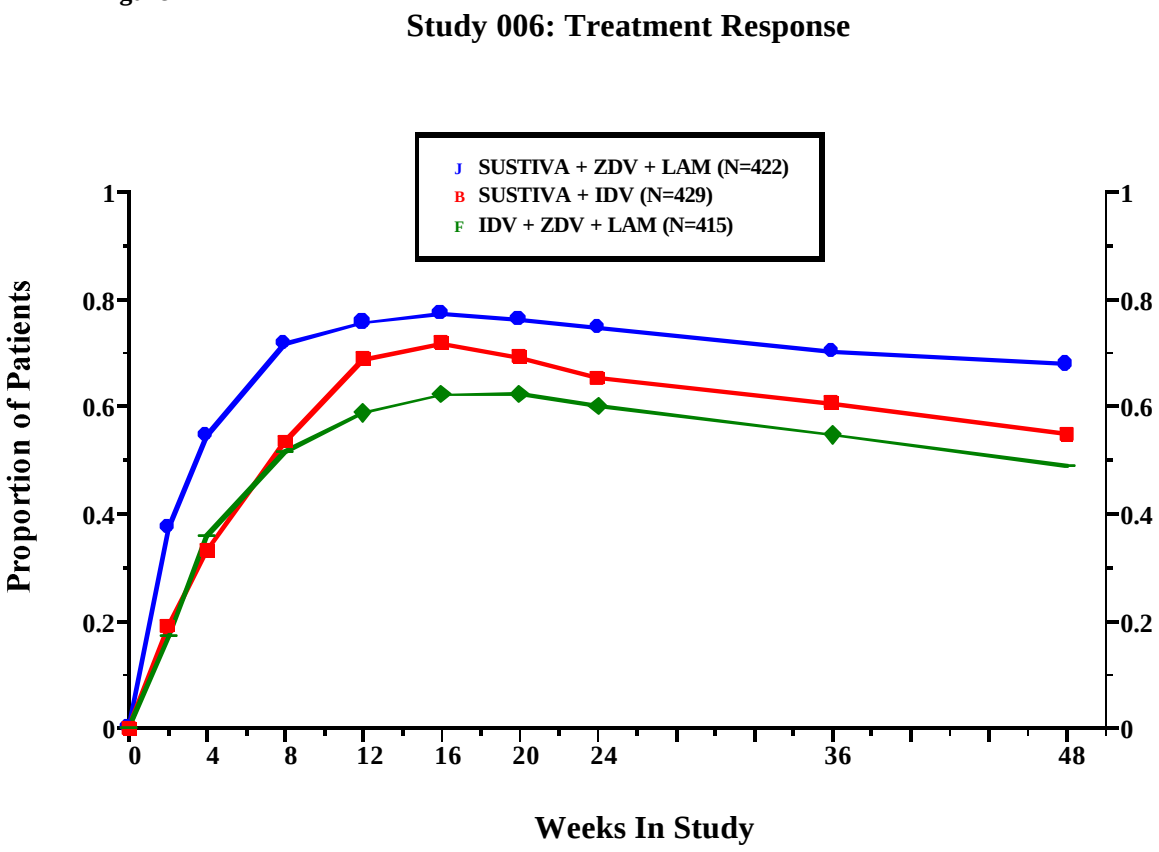
Description of Studies

In the two principle studies described below (Study 006 and ACTG 364), the response was measured as the time to treatment failure (TTF). Plasma HIV-RNA levels were quantified using the AMPLICOR HIV-1 RNA MONITOR™ (assay limit 400 copies/mL in Study 006 and 500 copies/mL in ACTG 364).

Study 006, an ongoing, randomized, open-label trial, compares SUSTIVA (600 mg once daily) + indinavir (IDV, 1000 mg q8h) or SUSTIVA (600 mg once daily) + zidovudine (ZDV, 300 mg q12h) + lamivudine (LAM, 150 mg q12h) 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-naïve at study entry. The mean baseline CD4 cell count was 341 cells/mm^3 and the mean

baseline HIV-RNA level was 60,250 copies/mL. There was no significant difference in mean CD4 cell count among the treatment groups; the overall mean increase was approximately 200 cells at 48 weeks among patients who continued on study regimens. Treatment response and outcomes through 48 weeks are shown in Figure 1 and Table 3, respectively.

Figure 1



- Proportion of patients at each time point who have HIV RNA <400 copies, are on their original study medication, and who have not experienced an AIDS-defining event.

Table 3 Study 006 - Outcomes of Randomized Treatment Through 48 Weeks

Outcome	SUSTIVA +ZDV+LAM N=422	SUSTIVA +IDV N=429	IDV +ZDV+LAM N=415
HIV-RNA <400 copies/mL (<50† copies/mL)	68% (62%)	55% (49%)	49% (43%)
HIV-RNA ≥400 copies/mL ††	6%	14%	11%
CDC Category C Event ††	3%	2%	2%
Discontinuations for Adverse Events ††*	8%	8%	17%
Discontinuations for Other Reasons††**	15%	22%	21%

† Ultrasensitive HIV-1 MONITOR™ assay

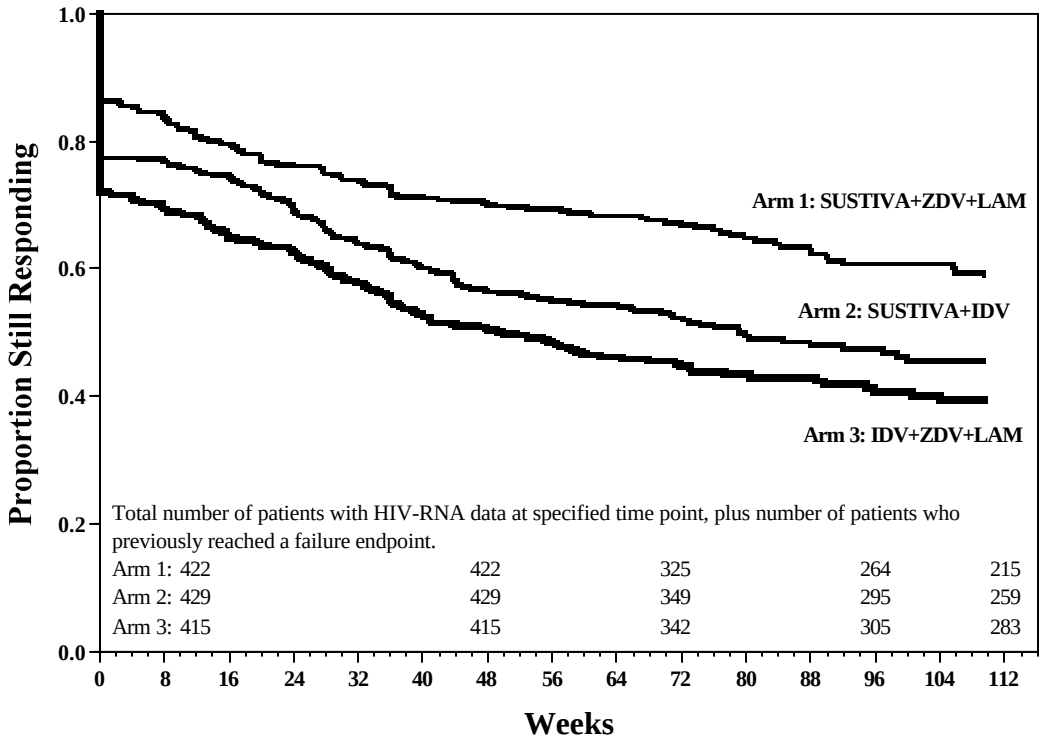
†† These rates reflect events that were counted as the initial reason for treatment failure in the analysis.

* See **ADVERSE REACTIONS** for a description of the safety profile of these regimens.

** Consent withdrawn, lost to follow-up, missing data or protocol violation

In addition to the complete 48-week follow-up data reported above, longer term data are shown in Figure 2. This analysis allows for the inclusion of data beyond 48 weeks as Kaplan-Meier estimates by accounting for patients who have not reached 112 weeks of follow-up.

Study 006: Time to Treatment Failure



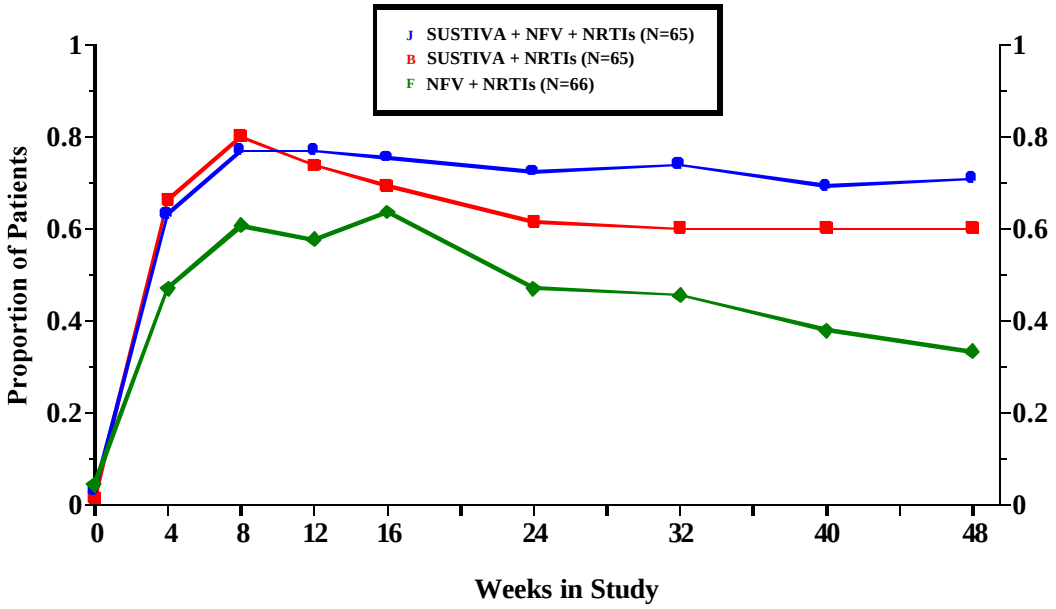
- Subjects were considered to have reached the study endpoint at the first time they either experienced virologic rebound (2 HIV-RNA values ≥400 copies), had an AIDS-defining clinical event, or discontinued study medication.

- Subjects who did not respond to initial treatment (no HIV-RNA values <400 copies) were considered to have reached this endpoint at time zero.

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 and ninety-six patients (mean age 41 years [range 18-76], 74% Caucasian, 88% male) received NRTIs in combination with SUSTIVA (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-RNA level was 8,130 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 response and outcomes are shown in Figure 3 and Table 4, respectively.

Figure 3

Study ACTG 364: Treatment Response



- Proportion of patients at each time point who have HIV-RNA <500 copies, are on their original study medication, and who have not experienced an AIDS-defining event.

Table 4 Study ACTG 364 - Outcomes of Randomized Treatment Through 48 Weeks

Outcome	SUSTIVA+NFV +NRTIs N=65	SUSTIVA +NRTIs N=65	NFV +NRTIs N=66
HIV-RNA <500 copies/mL	71%	60%	33%
HIV-RNA ≥500 copies/mL ††	17%	37%	62%
CDC Category C event ††	2%	0%	0%
Discontinuations for Adverse Events ††*	3%	3%	5%
Discontinuations for Other Reasons ††**	8%	0%	0%

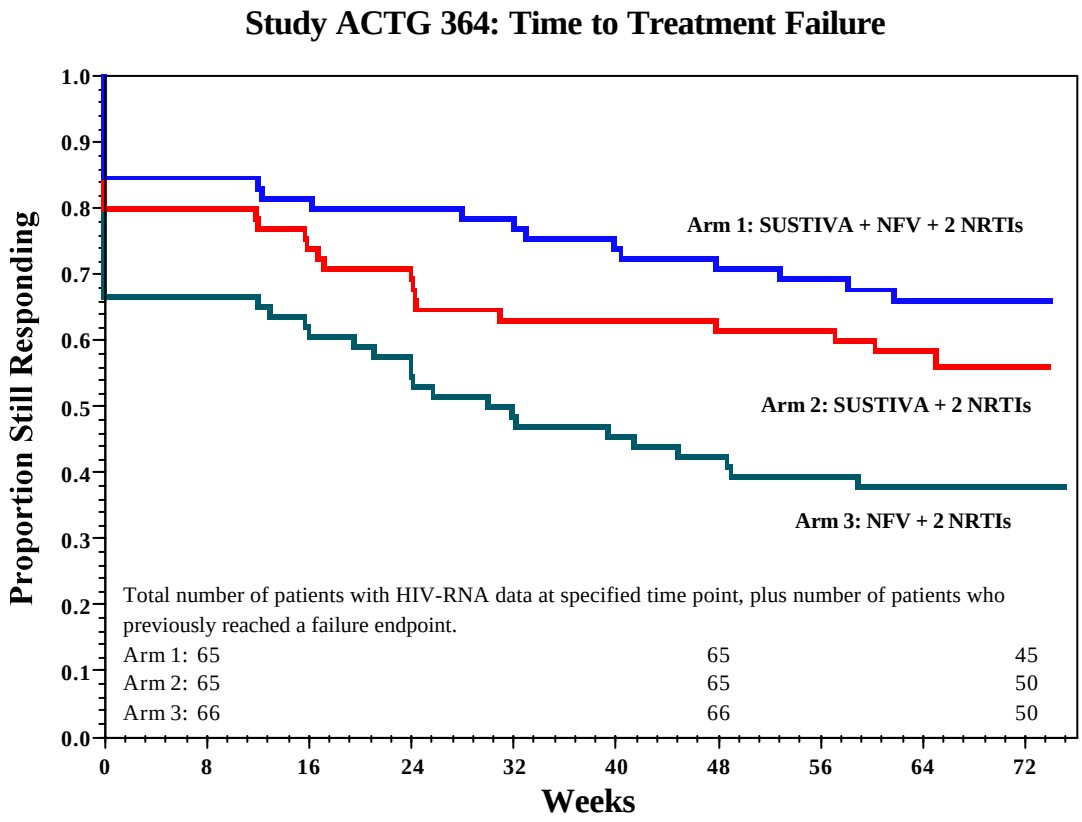
†† These rates reflect events that were counted as the initial reason for treatment failure in the analysis.

* See **ADVERSE REACTIONS** for a description of the safety profile of these regimens.

** Consent withdrawn, lost to follow-up, missing data or protocol violation

In addition to the complete 48-week data reported above, longer-term data are shown in Figure 4. This analysis allows for the inclusion of data beyond 48 weeks as Kaplan-Meier estimates by accounting for patients who have not reached 72 weeks of follow-up.

Figure 4



- Subjects were considered to have reached the study endpoint at the first time they either experienced virologic rebound (2 HIV-RNA values ≥500 copies), had an AIDS-defining clinical event, or discontinued study medication.
- Subjects who did not respond to initial treatment (no HIV-RNA values ≤500 copies) were considered to have reached this endpoint at time zero.
- The initial plateaus through week 12 are due to the virologic testing schedule and the lack of dropouts during this interval.

CONTRAINDICATIONS

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

WARNINGS

SUSTIVA must not be used as a single agent to treat HIV 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 and 635 patients treated with control regimens, the frequency of specific serious psychiatric events among patients who received SUSTIVA or control regimens, respectively, were: severe depression (0.9%, 0.5%), suicidal ideation/attempts (0.5%, 0.3%), aggressive behavior (0.3%, 0.3%), paranoid reactions (0.2%, 0.2%) and manic reactions (0.1%, 0%). Patients with a prior history of psychiatric disorders appear to be at greater risk for these serious psychiatric adverse experiences, with the frequency of each of the above events approximating 1%. There have also been occasional post marketing 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 5-9% in patients treated with regimens containing SUSTIVA and from 3-5% 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 improves the tolerability of these nervous system symptoms and is recommended during the first weeks of therapy and for 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 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.

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

PRECAUTIONS

General

Skin Rash: In controlled clinical trials, 26% (266/1008) of patients treated with 600 mg SUSTIVA experienced new onset skin rash compared with 17% (111/635) of patients treated in control groups. Rash associated with blistering, moist desquamation, or ulceration occurred in 0.9% (9/1008) of patients treated with SUSTIVA. The incidence of Grade 4 rash (e.g., 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 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 pediatric patients was eight 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 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 and triglycerides 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. 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 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 improves the tolerability of these symptoms, and these symptoms are likely to improve with continued therapy. Patients should be alerted to the potential for additive central nervous system effects when SUSTIVA is used concomitantly with alcohol or psychoactive drugs. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery (see **WARNINGS; Nervous System Symptoms**). In clinical trials, patients who develop central nervous system symptoms were not more likely to subsequently develop psychiatric symptoms (see **WARNINGS; Psychiatric Symptoms**).

Patients should also be informed that serious psychiatric symptoms including severe depression, suicide attempts, aggressive behavior, delusions, paranoia and psychosis-like symptoms have also been infrequently reported in patients receiving SUSTIVA. Patients should be informed that if they experience severe psychiatric adverse experiences they should seek immediate medical evaluation to assess the possibility that the symptoms may be related to the use of SUSTIVA, and if so, to determine whether discontinuation of SUSTIVA may be required. Patients should also inform their physician of any history of mental illness or substance abuse (**see WARNINGS; Psychiatric Symptoms**).

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

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

SUSTIVA may interact with some drugs; therefore, patients should be advised to report 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 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 (e.g., phenobarbital, rifampin, rifabutin) would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations. Drug interactions with SUSTIVA (efavirenz) are summarized in Table 5.

Table 5*

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 (200 mg), 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.

Amprenavir: SUSTIVA has the potential to decrease serum concentrations of amprenavir.

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. 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; Reproductive Risk Potential)**.

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.

There are no adequate and well-controlled studies in pregnant women. SUSTIVA (efavirenz) 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 26% of adults, and a higher frequency of Grade 3 or 4 rash reported in 7% (4/57) of pediatric patients compared to 0.9% of adults (see **ADVERSE REACTIONS; Table 7)**.

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

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

Table 6
Percent of Patients with One or More Selected Nervous System Symptoms [1,2]

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 [3]	33.3	15.6
Moderate Symptoms [4]	17.4	7.7
Severe Symptoms [5]	2.0	1.3
Treatment discontinuation as a result of symptoms	2.1	1.1

[1] Includes events reported regardless of causality.
[2] Data from Study 006 and three Phase 2/3 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.

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 (0.9%, 0.5%), suicidal ideation or attempts (0.5%, 0.3%), aggressive behavior (0.3%,

0.3%), paranoid reactions (0.2%, 0.2%) and manic reactions (0.1%, 0%) **(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 (10.0%, 8.2%), anxiety (8.2%, 5.5%), and nervousness (5.9%, 1.9%).

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 may be considered when SUSTIVA is restarted. SUSTIVA should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. The frequency of rash by NCI grade and the discontinuation rates as a result of rash are provided in Table 7.

Table 7
Percent of Patients with Treatment-Emergent Rash[1,2]

Percent of Patients with:	Description of Rash Grade[3]	SUSTIVA 600 mg Once Daily Adults (N=1008)	SUSTIVA Pediatric Patients (N=57)	Control Groups Adults (N= 635)
		%	%	%
Rash of Any Grade	-	26.3	40.3	17.5
Grade 1 Rash	Erythema, pruritus	10.7	8.8	9.8
Grade 2 Rash	Diffuse maculopapular rash, dry desquamation	14.7	24.5	7.4
Grade 3 Rash	Vesiculation, moist desquamation, ulceration	0.8	3.5	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

[1] Includes events reported regardless of causality.
[2] Data from Study 006 and three Phase 2/3 studies.
[3] NCI Grading System.

As seen in Table 7, rash is more common in pediatric patients 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.

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

Drug-related clinical adverse experiences of moderate or severe intensity observed in ≥2% of patients in three controlled clinical trials are presented in Table 8.

Table 8
Percent of Patients with Treatment-Emergent[1] Adverse Events of Moderate or Severe Intensity Reported in ≥2% of 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[2] + ZDV/LAM (N=412)	SUSTIVA[2] + Indinavir (N=415)	Indinavir + ZDV/LAM (N=401)	SUSTIVA[2] + Nelfinavir + NRTIs (N=64)	SUSTIVA[2] + NRTIs (N=65)	Nelfinavir + NRTIs (N=66)
	%	%	%	%	%	%
Body as a Whole						
Fatigue	7	5	8	0	2	3
Pain	1	1	5	13	6	17
Central and Peripheral Nervous System						
Dizziness	8	8	3	2	6	6
Headache	7	4	4	5	2	3
Concentration Impaired	5	2	0	0	0	0
Insomnia	6	7	3	0	0	2
Abnormal Dreams	3	1	0	--	--	--
Somnolence	3	2	2	0	0	0
Anorexia	1	0	1	0	2	2
Gastrointestinal						
Nausea	12	7	25	3	2	2
Vomiting	7	6	14	--	--	--
Diarrhea	6	8	6	14	3	9
Dyspepsia	3	3	5	0	0	2
Abdominal Pain	1	2	4	3	3	3
Psychiatric						
Anxiety	1	3	0	--	--	--
Depression	2	1	0	3	0	5
Nervousness	2	2	0	2	0	2
Skin & Appendages						
Rash	13	20	7	9	5	9
Pruritus	0	1	1	9	5	9
Increased Sweating	2	1	0	0	0	0

[1] 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.
[2] SUSTIVA provided as 600 mg Once Daily.
-- = Not Specified.

In Study 006, lipodystrophy was reported in 2.3% of patients treated with SUSTIVA (efavirenz) + IDV, 0.7% of patients treated with SUSTIVA+ZDV+LAM and 1.0% of patients treated with IDV+ZDV+LAM.

Clinical adverse experiences of moderate to severe intensity observed in ≥10% of 57 pediatric patients aged 3 to 16 years who received SUSTIVA, 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***).

Post-Marketing Experience:

Body as a Whole: allergic reactions, asthenia

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

Metabolic and Nutritional: hypercholesterolemia, hypertriglyceridemia

Musculoskeletal: arthralgia, myalgia, myopathy

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

Respiratory: dyspnea

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

Special Senses: abnormal vision, tinnitus

Laboratory Abnormalities:

Liver Enzymes: Among 1008 patients treated with 600 mg efavirenz in controlled clinical trials, 3% developed AST levels and 3% developed ALT levels greater than five times the upper limit of normal. Similar elevations of AST and ALT were seen in patients treated with control regimens.

Liver function tests should be monitored in patients with a prior history of Hepatitis B and/or C. In 156 patients treated with 600 mg of SUSTIVA who were seropositive for Hepatitis B and/or C, 7% developed AST levels and 8% developed ALT levels greater than five times the upper limit of normal. In 91 patients seropositive for Hepatitis B and/or C treated with control regimens, 5% developed AST elevations and 4% 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 10% of patients seropositive for Hepatitis B or C. In patients treated with control regimens, the incidence of GGT elevations to this level was 1.5-2%, 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. In patients treated with SUSTIVA+ZDV+LAM, increases in non-fasting total cholesterol and HDL of approximately 20% and 25%, respectively, were observed. In patients treated with SUSTIVA+IDV, increases in non-fasting cholesterol and HDL of approximately 40% and 35%, respectively, were observed. The effects of SUSTIVA on triglycerides and LDL were not well-characterized since samples were taken from non-fasting patients. The clinical significance of these findings is unknown (see **PRECAUTIONS; General**).

Serum Amylase: Asymptomatic elevations in serum amylase greater than 1.5 times the upper limit of normal were seen in 10% of patients treated with SUSTIVA and in 6% of patients treated with control regimens. The clinical significance of asymptomatic increases in serum amylase is unknown (**see ADVERSE REACTIONS**).

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 9 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 9
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

Bottles of 90 NDC 0056-0474-92

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

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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