* Sections or subsections omitted from the full prescribing information are not listed.

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

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

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

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

	Study 006 LAM-, NNRTI-, and Protease Inhibitor-Naive Patients			Study ACTG 364 NRTI-experienced, NNRTI-, and Protease Inhibitor-Naive Patients		
	SUSTIVA[b] + ZDV/LAM (n=412)	SUSTIVA[b] + Indinavir (n=415)	Indinavir + ZDV/LAM (n=401)	SUSTIVA[b] + Nelfinavir + NRTIs (n=64)	SUSTIVA[b] + NRTIs (n=65)	Nelfinavir + NRTIs (n=66)
Adverse Reactions	180 weeks[c]	102 weeks[c]	76 weeks[c]	71.1 weeks[c]	70.9 weeks[c]	62.7 weeks[c]
Skin & Appendages						
Rash[d]	11%	16%	5%	9%	5%	9%
Pruritus	<1%	1%	1%	9%	5%	9%

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

[b] SUSTIVA provided as 600 mg once daily.

[c] Median duration of treatment.

[d] Includes erythema multiforme, rash, rash erythematous, rash follicular, rash maculopapular, rash petechial, rash pustular, and urticaria for Study 006 and macules, papules, rash, erythema, redness, inflammation, allergic rash, urticaria, welts, hives, itchy, and pruritus for ACTG 364.

— = Not Specified.

ZDV = zidovudine, LAM = lamivudine.

Pancreatitis has been reported, although a causal relationship with efavirenz has not been established. Asymptomatic increases in serum amylase levels were observed in a significantly higher number of patients treated with efavirenz 600 mg than in control patients (see *Laboratory Abnormalities*).

Nervous System Symptoms

For 1008 patients treated with regimens containing SUSTIVA and 635 patients treated with a control regimen in controlled trials, Table 3 lists the frequency of symptoms of different degrees of severity and gives the discontinuation rates 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 [*see Warnings and Precautions (5.5)*]. The frequencies of specific central and peripheral nervous system symptoms are provided in Table 2.

Table 3: Percent of Patients with One or More Selected Nervous System Symptoms[a,b]

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

[a] Includes events reported regardless of causality.
[b] Data from Study 006 and three Phase 2/3 studies.
[c] "Mild" = Symptoms which do not interfere with patient's daily activities.
[d] "Moderate" = Symptoms which may interfere with daily activities.
[e] "Severe" = Events which interrupt patient's usual daily activities.

Psychiatric Symptoms

Serious psychiatric adverse experiences have been reported in patients treated with SUSTIVA. In controlled trials, psychiatric symptoms observed at a frequency greater than 2% among patients treated with SUSTIVA or control regimens, respectively, were depression (19%, 16%), anxiety (13%, 9%), and nervousness (7%, 2%).

Rash

In controlled clinical trials, the frequency of rash (all grades, regardless of causality) was 26% for 1008 adults treated with regimens containing SUSTIVA and 17% for 635 adults treated with a control regimen. Most reports of rash were mild or moderate in severity. The frequency of Grade 3 rash was 0.8% for SUSTIVA-treated patients and 0.3% for control groups, and the frequency of Grade 4 rash was 0.1% for SUSTIVA and 0 for control groups. The discontinuation rates as a result of rash were 1.7% for SUSTIVA-treated patients and 0.3% for control groups [*see Warnings and Precautions (5.7)*].

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.

Laboratory Abnormalities

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

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

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

[a] SUSTIVA provided as 600 mg once daily.

[b] Median duration of treatment.

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

[d] Nonfasting.

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

Patients Coinfected with Hepatitis B or C

Liver function tests should be monitored in patients with a history of hepatitis B and/or C. In the long-term data set from Study 006, 137 patients treated with SUSTIVA-containing regimens (median duration of therapy, 68 weeks) and 84 treated with a control regimen (median duration, 56 weeks) were seropositive at screening for hepatitis B (surface antigen positive) and/or C (hepatitis C antibody positive). Among these coinfected patients, elevations in AST to greater than five times ULN developed in 13% of patients in the SUSTIVA arms and 7% of those in the control arm, and elevations in ALT to greater than five times ULN developed in 20% of patients in the SUSTIVA arms and 7% of patients in the control arm. Among coinfected patients, 3% of those treated with SUSTIVA-containing regimens and 2% in the control arm discontinued from the study because of liver or biliary system disorders [*see Warnings and Precautions (5.8)*].

Lipids

Increases from baseline in total cholesterol of 10-20% have been observed in some uninfected volunteers receiving SUSTIVA. In patients treated with SUSTIVA + zidovudine + lamivudine, increases from baseline in nonfasting total cholesterol and HDL of approximately 20% and 25%, respectively, were observed. In patients treated with SUSTIVA + indinavir, increases from baseline in nonfasting cholesterol and HDL of approximately 40% and 35%, respectively, were observed. Nonfasting total cholesterol levels ≥240 mg/dL and ≥300 mg/dL were reported in 34% and 9%, respectively, of patients treated with SUSTIVA + zidovudine + lamivudine; 54% and 20%, respectively, of patients treated with SUSTIVA + indinavir; and 28% and 4%, respectively, of patients treated with indinavir + zidovudine + lamivudine. The effects of SUSTIVA on triglycerides and LDL in this study were not well characterized since samples were taken from nonfasting patients. The clinical significance of these findings is unknown [*see Warnings and Precautions (5.10)*].

6.2 Clinical Trial Experience in Pediatric Patients

Because clinical studies are conducted under widely varying conditions, the adverse reaction rates reported cannot be directly compared to rates in other clinical studies and may not reflect the rates observed in clinical practice.

Assessment of adverse reactions is based on three clinical trials in 182 HIV-1 infected pediatric patients (3 months to 21 years of age) who received SUSTIVA in combination with other antiretroviral agents for a median of 123 weeks. The adverse reactions observed in the three trials were similar to those observed in clinical trials in adults except that rash was more common in pediatric patients (32% for all grades regardless of causality) and more often of higher grade (ie, more severe). Two (1.1%) pediatric patients experienced Grade 3 rash (confluent rash with fever, generalized rash), and four (2.2%) pediatric patients had Grade 4 rash (all erythema multiforme). Five pediatric patients (2.7%) discontinued from the study because of rash [*see Warnings and Precautions (5.7)*].

6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of SUSTIVA. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: allergic reactions, asthenia, redistribution/accumulation of body fat [*see Warnings and Precautions (5.12)*]

Central and Peripheral Nervous System: abnormal coordination, ataxia, cerebellar coordination and balance disturbances, convulsions, hypoesthesia, paresthesia, neuropathy, tremor, vertigo

Endocrine: gynecomastia

Gastrointestinal: constipation, malabsorption

Cardiovascular: flushing, palpitations

Liver and Biliary System: hepatic enzyme increase, hepatic failure, hepatitis. A few of the postmarketing reports of hepatic failure, including cases in patients

with no pre-existing hepatic disease or other identifiable risk factors, were characterized by a fulminant course, progressing in some cases to transplantation or death.

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, photoallergic dermatitis, Stevens-Johnson syndrome

Special Senses: abnormal vision, tinnitus

7 DRUG INTERACTIONS

7.1 Drug-Drug Interactions

Efavirenz has been shown *in vivo* to induce CYP3A and CYP2B6. Other compounds that are substrates of CYP3A or CYP2B6 may have decreased plasma concentrations when coadministered with SUSTIVA. Drugs that induce CYP3A activity (eg, phenobarbital, rifampin, rifabutin) would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations [*see Dosage and Administration (2.1)*]. Drug interactions with SUSTIVA are summarized in Table 5 [for pharmacokinetics data *see Clinical Pharmacology (12.3, Tables 7* and *8)*]. This table includes potentially significant interactions, but is not all inclusive.

Table 5: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect	Clinical Comment
HIV antiviral agents		
Protease inhibitor: Fosamprenavir calcium	↓ amprenavir	Fosamprenavir (unboosted): Appropriate doses of the combinations with respect to safety and efficacy have not been established. Fosamprenavir/ritonavir: An additional 100 mg/day (300 mg total) of ritonavir is recommended when SUSTIVA is administered with fosamprenavir/ritonavir once daily. No change in the ritonavir dose is required when SUSTIVA is administered with fosamprenavir plus ritonavir twice daily.
Protease inhibitor: Atazanavir sulfate	↓ atazanavir*	*Treatment-naive patients:* When coadministered with SUSTIVA, the recommended dose of atazanavir is 400 mg with ritonavir 100 mg (together once daily with food) and SUSTIVA 600 mg (once daily on an empty stomach, preferably at bedtime). *Treatment-experienced patients:* Coadministration of SUSTIVA and atazanavir is not recommended.
Protease inhibitor: Indinavir	↓ indinavir*	The optimal dose of indinavir, when given in combination with SUSTIVA, is not known. Increasing the indinavir dose to 1000 mg every 8 hours does not compensate for the increased indinavir metabolism due to SUSTIVA. When indinavir at an increased dose (1000 mg every 8 hours) was given with SUSTIVA (600 mg once daily), the indinavir AUC and C_{min} were decreased on average by 33-46% and 39-57%, respectively, compared to when indinavir (800 mg every 8 hours) was given alone.
Protease inhibitor: Lopinavir/ritonavir	↓ lopinavir*	Dose increase of lopinavir/ritonavir is recommended for all patients. Lopinavir/ritonavir tablets should not be administered once daily in combination with SUSTIVA. See the lopinavir/ritonavir prescribing information for dose adjustments of lopinavir/ritonavir when coadministered with efavirenz in adult and pediatric patients.
Protease inhibitor: Ritonavir	↑ ritonavir* ↑ efavirenz*	When ritonavir 500 mg q12h was coadministered with SUSTIVA 600 mg once daily, the combination was associated with a higher frequency of adverse clinical experiences (eg, dizziness, nausea, paresthesia) and laboratory abnormalities (elevated liver enzymes). Monitoring of liver enzymes is recommended when SUSTIVA is used in combination with ritonavir.
Protease inhibitor: Saquinavir	↓ saquinavir*	Appropriate doses of the combination of SUSTIVA and saquinavir/ritonavir with respect to safety and efficacy have not been established.
NNRTI: Other NNRTIs	↑ or ↓ efavirenz and/or NNRTI	Combining two NNRTIs has not been shown to be beneficial. SUSTIVA should not be coadministered with other NNRTIs.

Table 5: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect	Clinical Comment
CCR5 co-receptor antagonist: Maraviroc	↓ maraviroc*	Refer to the full prescribing information for maraviroc for guidance on coadministration with efavirenz.
Integrase strand transfer inhibitor: Raltegravir	↓ raltegravir*	SUSTIVA reduces plasma concentrations of raltegravir. The clinical significance of this interaction has not been directly assessed.
Hepatitis C antiviral agents		
Protease inhibitor: Boceprevir	↓ boceprevir*	Plasma trough concentrations of boceprevir were decreased when boceprevir was coadministered with SUSTIVA, which may result in loss of therapeutic effect. The combination should be avoided.
Protease inhibitor: Telaprevir	↓ telaprevir* ↓ efavirenz*	Concomitant administration of telaprevir and SUSTIVA resulted in reduced steady-state exposures to telaprevir and efavirenz.
Other agents		
Anticoagulant: Warfarin	↑ or ↓ warfarin	Plasma concentrations and effects potentially increased or decreased by SUSTIVA.
Anticonvulsants:		
Carbamazepine	↓ carbamazepine* ↓ efavirenz*	There are insufficient data to make a dose recommendation for efavirenz. Alternative anticonvulsant treatment should be used.
Phenytoin Phenobarbital	↓ anticonvulsant ↓ efavirenz	Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.
Antidepressants: Bupropion	↓ bupropion*	The effect of efavirenz on bupropion exposure is thought to be due to the induction of bupropion metabolism. Increases in bupropion dosage should be guided by clinical response, but the maximum recommended dose of bupropion should not be exceeded.
Sertraline	↓ sertraline*	Increases in sertraline dosage should be guided by clinical response.

Table 5: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect	Clinical Comment
Antifungals:		
Voriconazole	↓ voriconazole* ↑ efavirenz*	SUSTIVA and voriconazole must not be coadministered at standard doses. Efavirenz significantly decreases voriconazole plasma concentrations, and coadministration may decrease the therapeutic effectiveness of voriconazole. Also, voriconazole significantly increases efavirenz plasma concentrations, which may increase the risk of SUSTIVA-associated side effects. When voriconazole is coadministered with SUSTIVA, voriconazole maintenance dose should be increased to 400 mg every 12 hours and SUSTIVA dose should be decreased to 300 mg once daily using the capsule formulation. SUSTIVA tablets should not be broken. [*See Dosage and Administration (2.1)* and *Clinical Pharmacology (12.3, Tables 8* and *9)*.]
Itraconazole	↓ itraconazole* ↓ hydroxyitraconazole*	Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered.
Ketoconazole	↓ ketoconazole	Drug interaction studies with SUSTIVA and ketoconazole have not been conducted. SUSTIVA has the potential to decrease plasma concentrations of ketoconazole.
Posaconazole	↓ posaconazole*	Avoid concomitant use unless the benefit outweighs the risks.
Anti-infective:		
Clarithromycin	↓ clarithromycin* ↑ 14-OH metabolite*	Plasma concentrations decreased by SUSTIVA; clinical significance unknown. In uninfected volunteers, 46% developed rash while receiving SUSTIVA and clarithromycin. No dose adjustment of SUSTIVA is recommended when given with clarithromycin. Alternatives to clarithromycin, such as azithromycin, should be considered (see *Other Drugs*, following table). Other macrolide antibiotics, such as erythromycin, have not been studied in combination with SUSTIVA.
Antimycobacterials:		
Rifabutin	↓ rifabutin*	Increase daily dose of rifabutin by 50%. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week.
Rifampin	↓ efavirenz*	If SUSTIVA is coadministered with rifampin to patients weighing 50 kg or more, an increase in the dose of SUSTIVA to 800 mg once daily is recommended.
Antimalarials:		
Artemether/ lumefantrine	↓ artemether* ↓ dihydroartemisinin* ↓ lumefantrine*	Artemether/lumefantrine should be used cautiously with efavirenz because decreased artemether, dihydroartemisinin (active metabolite of artemether), and/or lumefantrine concentrations may result in a decrease of antimalarial efficacy of artemether/lumefantrine.

Table 5: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect	Clinical Comment
Calcium channel blockers: Diltiazem	↓ diltiazem* ↓ desacetyl diltiazem* ↓ N-monodesmethyl diltiazem*	Diltiazem dose adjustments should be guided by clinical response (refer to the full prescribing information for diltiazem). No dose adjustment of efavirenz is necessary when administered with diltiazem.
Others (eg, felodipine, nicardipine, nifedipine, verapamil)	↓ calcium channel blocker	No data are available on the potential interactions of efavirenz with other calcium channel blockers that are substrates of CYP3A. The potential exists for reduction in plasma concentrations of the calcium channel blocker. Dose adjustments should be guided by clinical response (refer to the full prescribing information for the calcium channel blocker).
HMG-CoA reductase inhibitors: Atorvastatin Pravastatin Simvastatin	 ↓ atorvastatin* ↓ pravastatin* ↓ simvastatin*	Plasma concentrations of atorvastatin, pravastatin, and simvastatin decreased. Consult the full prescribing information for the HMG-CoA reductase inhibitor for guidance on individualizing the dose.

Table 5: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect	Clinical Comment
Hormonal contraceptives: Oral Ethinyl estradiol/ Norgestimate	↓ active metabolites of norgestimate*	A reliable method of barrier contraception must be used in addition to hormonal contraceptives. Efavirenz had no effect on ethinyl estradiol concentrations, but progestin levels (norelgestromin and levonorgestrel) were markedly decreased. No effect of ethinyl estradiol/norgestimate on efavirenz plasma concentrations was observed.
Implant Etonogestrel	↓ etonogestrel	A reliable method of barrier contraception must be used in addition to hormonal contraceptives. The interaction between etonogestrel and efavirenz has not been studied. Decreased exposure of etonogestrel may be expected. There have been postmarketing reports of contraceptive failure with etonogestrel in efavirenz-exposed patients.
Immunosuppressants: Cyclosporine, tacrolimus, sirolimus, and others metabolized by CYP3A	↓ immunosuppressant	Decreased exposure of the immunosuppressant may be expected due to CYP3A induction. These immunosuppressants are not anticipated to affect exposure of efavirenz. Dose adjustments of the immunosuppressant may be required. Close monitoring of immunosuppressant concentrations for at least 2 weeks (until stable concentrations are reached) is recommended when starting or stopping treatment with efavirenz.
Narcotic analgesic: Methadone	↓ methadone*	Coadministration in HIV-infected individuals with a history of injection drug use resulted in decreased plasma levels of methadone and signs of opiate withdrawal. Methadone dose was increased by a mean of 22% to alleviate withdrawal symptoms. Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.

* The interaction between SUSTIVA and the drug was evaluated in a clinical study. All other drug interactions shown are predicted.

This table is not all-inclusive.

Other Drugs

Based on the results of drug interaction studies [*see Clinical Pharmacology (12.3, Tables 7* and *8)*], no dosage adjustment is recommended when SUSTIVA is given with the following: aluminum/magnesium hydroxide antacids, azithromycin, cetirizine, famotidine, fluconazole, lamivudine, lorazepam, nelfinavir, paroxetine, tenofovir disoproxil fumarate, and zidovudine.

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

7.2 Cannabinoid Test Interaction

Efavirenz does not bind to cannabinoid receptors. False-positive urine cannabinoid test results have been reported with some screening assays in uninfected and HIV-infected subjects receiving efavirenz. Confirmation of positive screening tests for cannabinoids by a more specific method is recommended.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D: See *Warnings and Precautions (5.6).*

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 1-800-258-4263.

As of July 2010, the Antiretroviral Pregnancy Registry has received prospective reports of 792 pregnancies exposed to efavirenz-containing regimens, nearly all of which were first-trimester exposures (718 pregnancies). Birth defects occurred in 17 of 604 live births (first-trimester exposure) and 2 of 69 live births (second/third-trimester exposure). One of these prospectively reported defects with first-trimester exposure was a neural tube defect. A single case of anophthalmia with first-trimester exposure to efavirenz has also been prospectively reported; however, this case included severe oblique facial clefts and amniotic banding, a known association with anophthalmia. There have been six retrospective reports of findings consistent with neural tube defects, including meningomyelocele. All mothers were exposed to efavirenz-containing regimens in the first trimester. Although a causal relationship of these events to the use of

SUSTIVA has not been established, similar defects have been observed in preclinical studies of efavirenz.

Animal Data

Effects of efavirenz on embryo-fetal development have been studied in three nonclinical species (cynomolgus monkeys, rats, and rabbits). In monkeys, efavirenz 60 mg/kg/day was administered to pregnant females throughout pregnancy (gestation days 20 through 150). The maternal systemic drug exposures (AUC) were 1.3 times the exposure in humans at the recommended clinical dose (600 mg/day), with fetal umbilical venous drug concentrations approximately 0.7 times the maternal values. Three fetuses of 20 fetuses/infants had one or more malformations; there were no malformed fetuses or infants from placebo-treated mothers. The malformations that occurred in these three monkey fetuses included anencephaly and unilateral anophthalmia in one fetus, microphthalmia in a second, and cleft palate in the third. There was no NOAEL (no observable adverse effect level) established for this study because only one dosage was evaluated. In rats, efavirenz was administered either during organogenesis (gestation days 7 to 18) or from gestation day 7 through lactation day 21 at 50, 100, or 200 mg/kg/day. Administration of 200 mg/kg/day in rats was associated with increase in the incidence of early resorptions; and doses 100 mg/kg/day and greater were associated with early neonatal mortality. The AUC at the NOAEL (50 mg/kg/day) in this rat study was 0.1 times that in humans at the recommended clinical dose. Drug concentrations in the milk on lactation day 10 were approximately 8 times higher than those in maternal plasma. In pregnant rabbits, efavirenz was neither embryo lethal nor teratogenic when administered at doses of 25, 50, and 75 mg/kg/day over the period of organogenesis (gestation days 6 through 18). The AUC at the NOAEL (75 mg/kg/day) in rabbits was 0.4 times that in humans at the recommended clinical dose.

8.3 Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Efavirenz has been shown to pass into human breast milk. Because of the potential for HIV transmission and the potential for serious adverse effects in

nursing infants, mothers should be instructed not to breastfeed if they are receiving SUSTIVA.

8.4 Pediatric Use

The safety, pharmacokinetic profile, and virologic and immunologic responses of SUSTIVA were evaluated in antiretroviral-naive and -experienced HIV-1 infected pediatric patients 3 months to 21 years of age in three open-label clinical trials [*see Adverse Reactions (6.2), Clinical Pharmacology (12.3),* and *Clinical Studies (14.2)*]. The type and frequency of adverse reactions in these trials were generally similar to those of adult patients with the exception of a higher frequency of rash, including a higher frequency of Grade 3 or 4 rash, in pediatric patients compared to adults [*see Warnings and Precautions (5.7)* and *Adverse Reactions (6.2)*].

Use of SUSTIVA in patients younger than 3 months of age OR less than 3.5 kg body weight is not recommended because the safety, pharmacokinetics, and antiviral activity of SUSTIVA have not been evaluated in this age group and there is a risk of developing HIV resistance if SUSTIVA is underdosed. See *Dosage and Administration (2.2)* for dosing recommendations for pediatric patients.

8.5 Geriatric Use

Clinical studies of SUSTIVA did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other therapy.

8.6 Hepatic Impairment

SUSTIVA is not recommended for patients with moderate or severe hepatic impairment because there are insufficient data to determine whether dose adjustment is necessary. Patients with mild hepatic impairment may be treated with efavirenz without any adjustment in dose. 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 [*see Warnings and Precautions (5.8)* and *Clinical Pharmacology (12.3)*].

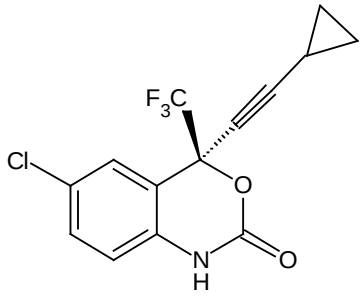
10 OVERDOSAGE

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.

11 DESCRIPTION

SUSTIVA® (efavirenz) is an HIV-1 specific, non-nucleoside, reverse transcriptase inhibitor (NNRTI). 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 microgram/mL).

Capsules: SUSTIVA is available as capsules for oral administration containing either 50 mg or 200 mg of efavirenz and the following inactive ingredients: lactose monohydrate, magnesium stearate, sodium lauryl sulfate, and sodium

starch glycolate. The capsule shell contains the following inactive ingredients and dyes: gelatin, sodium lauryl sulfate, titanium dioxide, and/or yellow iron oxide. The capsule shells may also contain silicon dioxide. The capsules are printed with ink containing carmine 40 blue, FD&C Blue No. 2, and titanium dioxide.

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Efavirenz is an antiviral drug [*see Microbiology (12.4)*].

12.3 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-1-infected patients at steady state, mean C_{max}, mean C_{min}, and mean AUC were dose proportional following 200 mg, 400 mg, and 600 mg daily doses. Time-to-peak plasma concentrations were approximately 3-5 hours and steady-state plasma concentrations were reached in 6-10 days. In 35 patients receiving SUSTIVA 600 mg once daily, steady-state C_{max} was 12.9 ± 3.7 μM (mean ± SD), steady-state C_{min} was 5.6 ± 3.2 μM, and AUC was 184 ± 73 μM•h.

Effect of Food on Oral Absorption:

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

Tablets: Administration of a single 600 mg efavirenz tablet with a high-fat/high-caloric meal (approximately 1000 kcal, 500-600 kcal from fat) was associated with a 28% increase in mean AUC_{∞} of efavirenz and a 79% increase in mean C_{max} of efavirenz relative to the exposures achieved under fasted conditions. [*See Dosage and Administration (2)* and *Patient Counseling Information (17).*]

Bioavailability of capsule contents mixed with food vehicles: In healthy adult subjects, the efavirenz AUC when administered as the contents of three 200 mg capsules mixed with 2 teaspoons of certain food vehicles (applesauce, grape jelly or yogurt, or infant formula) met bioequivalency criteria for the AUC of the intact capsule formulation administered under fasted conditions.

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 CYP3A and CYP2B6 are the major isozymes responsible for efavirenz metabolism.

Efavirenz has been shown to induce CYP 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

Pediatric: The pharmacokinetic parameters for efavirenz at steady state in pediatric patients were predicted by a population pharmacokinetic model and are summarized in Table 6 by weight ranges that correspond to the recommended doses.

Table 6: Predicted Steady-State Pharmacokinetics of Recommended Doses of Efavirenz (Capsules/Capsule Sprinkles) in HIV-Infected Pediatric Patients

Body Weight	Dose	Mean $AUC_{(0-24)}$ μM·h	Mean C_{max} μg/mL	Mean C_{min} μg/mL
3.5-5 kg	100 mg	220.52	5.81	2.43
5-7.5 kg	150 mg	262.62	7.07	2.71
7.5-10 kg	200 mg	284.28	7.75	2.87
10-15 kg	200 mg	238.14	6.54	2.32
15-20 kg	250 mg	233.98	6.47	2.3
20-25 kg	300 mg	257.56	7.04	2.55

Table 6: Predicted Steady-State Pharmacokinetics of Recommended Doses of Efavirenz (Capsules/Capsule Sprinkles) in HIV-Infected Pediatric Patients

Body Weight	Dose	Mean $AUC_{(0-24)}$ μM·h	Mean C_{max} μg/mL	Mean C_{min} μg/mL
25-32.5 kg	350 mg	262.37	7.12	2.68
32.5-40 kg	400 mg	259.79	6.96	2.69
>40 kg	600 mg	254.78	6.57	2.82

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

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.

Hepatic impairment: A multiple-dose study showed no significant effect on efavirenz pharmacokinetics in patients with mild hepatic impairment (Child-Pugh Class A) compared with controls. There were insufficient data to determine whether moderate or severe hepatic impairment (Child-Pugh Class B or C) affects efavirenz pharmacokinetics.

Drug Interaction Studies

Efavirenz has been shown *in vivo* to cause hepatic enzyme induction, thus increasing the biotransformation of some drugs metabolized by CYP3A and CYP2B6. *In vitro* studies have shown that efavirenz inhibited CYP isozymes 2C9 and 2C19 with K_i values (8.5-17 μM) in the range of observed efavirenz plasma concentrations. In *in vitro* studies, efavirenz did not inhibit CYP2E1 and inhibited CYP2D6 and CYP1A2 (K_i values 82-160 μM) only at concentrations well above those achieved clinically. Coadministration of efavirenz with drugs primarily metabolized by CYP2C9, CYP2C19, CYP3A, or CYP2B6 isozymes may result in altered plasma concentrations of the coadministered drug. Drugs which induce CYP3A and CYP2B6 activity would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations.

Reference ID: 3512480

Drug interaction studies were performed with efavirenz and other drugs likely to be coadministered or drugs commonly used as probes for pharmacokinetic interaction. The effects of coadministration of efavirenz on the C_{max}, AUC, and C_{min} are summarized in Table 7 (effect of efavirenz on other drugs) and Table 8 (effect of other drugs on efavirenz). For information regarding clinical recommendations see *Drug Interactions (7.1)*.

Table 7: Effect of Efavirenz on Coadministered Drug Plasma C_{max}, AUC, and C_{min}

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Coadministered Drug (mean % change) C_{max} (90% CI)	AUC (90% CI)	C_{min} (90% CI)
Atazanavir	400 mg qd with a light meal d 1-20	600 mg qd with a light meal d 7-20	27	↓ 59% (49-67%)	↓ 74% (68-78%)	↓ 93% (90-95%)
	400 mg qd d 1-6, then 300 mg qd d 7-20 with ritonavir 100 mg qd and a light meal	600 mg qd 2 h after atazanavir and ritonavir d 7-20	13	↑ 14%[a] (↓ 17-↑ 58%)	↑ 39%[a] (2-88%)	↑ 48%[a] (24-76%)
	300 mg qd/ritonavir 100 mg qd d 1-10 (pm), then 400 mg qd/ritonavir 100 mg qd d 11-24 (pm) (simultaneous with efavirenz)	600 mg qd with a light snack d 11-24 (pm)	14	↑ 17% (8-27%)	↔	↓ 42% (31-51%)
Indinavir	1000 mg q8h × 10 days	600 mg qd × 10 days	20			
	After morning dose			↔[b]	↓ 33%[b] (26-39%)	↓ 39%[b] (24-51%)
	After afternoon dose			↔[b]	↓ 37%[b] (26-46%)	↓ 52%[b] (47-57%)
	After evening dose			↓ 29%[b] (11-43%)	↓ 46%[b] (37-54%)	↓ 57%[b] (50-63%)
Lopinavir/ ritonavir	400/100 mg capsule q12h × 9 days	600 mg qd × 9 days	11,7[c]	↔[d]	↓ 19%[d] (↓ 36-↑ 3%)	↓ 39%[d] (3-62%)
	500/125 mg tablet q12h × 10 days with efavirenz compared to 400/100 mg q12h alone	600 mg qd × 9 days	19	↑ 12%[d] (2-23%)	↔[d]	↓ 10%[d] (↓ 22-↑ 4%)
	600/150 mg tablet q12h × 10 days with efavirenz compared to 400/100 mg q12h alone	600 mg qd × 9 days	23	↑ 36%[d] (28-44%)	↑ 36%[d] (28-44%)	↑ 32%[d] (21-44%)
Nelfinavir	750 mg q8h × 7 days	600 mg qd × 7 days	10	↑ 21% (10-33%)	↑ 20% (8-34%)	↔

Reference ID: 3512480

Table 7: Effect of Efavirenz on Coadministered Drug Plasma C_{max}, AUC, and C_{min}

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Coadministered Drug (mean % change) C_{max} (90% CI)	AUC (90% CI)	C_{min} (90% CI)
Metabolite AG-1402				↓ 40% (30-48%)	↓ 37% (25-48%)	↓ 43% (21-59%)
Ritonavir	500 mg q12h × 8 days	600 mg qd × 10 days	11			
	After AM dose			↑ 24% (12-38%)	↑ 18% (6-33%)	↑ 42% (9-86%)[e]
	After PM dose			↔	↔	↑ 24% (3-50%)[e]
Saquinavir SGC[f]	1200 mg q8h × 10 days	600 mg qd × 10 days	12	↓ 50% (28-66%)	↓ 62% (45-74%)	↓ 56% (16-77%)[e]
Lamivudine	150 mg q12h × 14 days	600 mg qd × 14 days	9	↔	↔	↑ 265% (37-873%)
Tenofovir[g]	300 mg qd	600 mg qd × 14 days	29	↔	↔	↔
Zidovudine	300 mg q12h × 14 days	600 mg qd × 14 days	9	↔	↔	↑ 225% (43-640%)
Maraviroc	100 mg bid	600 mg qd	12	↓ 51% (37-62%)	↓ 45% (38-51%)	↓ 45% (28-57%)
Raltegravir	400 mg single dose	600 mg qd	9	↓ 36% (2-59%)	↓ 36% (20-48%)	↓ 21% (↓ 51-↑ 28%)
Boceprevir	800 mg tid × 6 days	600 mg qd × 16 days	NA	↓ 8% (↓ 22-↑ 8%)	↓ 19% (11-25%)	↓ 44% (26-58%)
Telaprevir	750 mg q8h × 10 days	600 mg qd × 20 days	21	↓ 9% (↓ 18-↑ 2%)	↓ 26% (16-35%)	↓ 47% (35-56%)
Azithromycin	600 mg single dose	400 mg qd × 7 days	14	↑ 22% (4-42%)	↔	NA
Clarithromycin	500 mg q12h × 7 days	400 mg qd × 7 days	11	↓ 26% (15-35%)	↓ 39% (30-46%)	↓ 53% (42-63%)
14-OH metabolite				↑ 49% (32-69%)	↑ 34% (18-53%)	↑ 26% (9-45%)
Fluconazole	200 mg × 7 days	400 mg qd × 7 days	10	↔	↔	↔
Itraconazole	200 mg q12h × 28 days	600 mg qd × 14 days	18	↓ 37% (20-51%)	↓ 39% (21-53%)	↓ 44% (27-58%)
Hydroxy-itraconazole				↓ 35% (12-52%)	↓ 37% (14-55%)	↓ 43% (18-60%)
Posaconazole	400 mg (oral suspension) bid × 10 and 20 days	400 mg qd × 10 and 20 days	11	↓ 45% (34-53%)	↓ 50% (40-57%)	NA
Rifabutin	300 mg qd × 14 days	600 mg qd × 14 days	9	↓ 32% (15-46%)	↓ 38% (28-47%)	↓ 45% (31-56%)
Voriconazole	400 mg po q12h × 1 day, then 200 mg po q12h × 8 days	400 mg qd × 9 days	NA	↓ 61%[h]	↓ 77%[h]	NA
	300 mg po q12h	300 mg qd × 7 days	NA	↓ 36%[i]	↓ 55%[i]	NA

Reference ID: 3512480

Table 7: Effect of Efavirenz on Coadministered Drug Plasma C_{max}, AUC, and C_{min}

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Coadministered Drug (mean % change) C_{max} (90% CI)	AUC (90% CI)	C_{min} (90% CI)
	days 2-7			(21-49%)	(45-62%)	
	400 mg po q12h days 2-7	300 mg qd × 7 days	NA	↑ 23%[i] (↓ 1-↑ 53%)	↓ 7%[i] (↓ 23-↑ 13%)	NA
Artemether/ lumefantrine	Artemether 20 mg/ lumefantrine 120 mg tablets (6 4-tablet doses over 3 days)	600 mg qd × 26 days	12			
Artemether				↓ 21%	↓ 51%	NA
dihydroartemisinin				↓ 38%	↓ 46%	NA
lumefantrine				↔	↓ 21%	NA
Atorvastatin	10 mg qd × 4 days	600 mg qd × 15 days	14	↓ 14% (1-26%)	↓ 43% (34-50%)	↓ 69% (49-81%)
Total active (including metabolites)				↓ 15% (2-26%)	↓ 32% (21-41%)	↓ 48% (23-64%)
Pravastatin	40 mg qd × 4 days	600 mg qd × 15 days	13	↓ 32% (↓ 59-↑ 12%)	↓ 44% (26-57%)	↓ 19% (0-35%)
Simvastatin	40 mg qd × 4 days	600 mg qd × 15 days	14	↓ 72% (63-79%)	↓ 68% (62-73%)	↓ 45% (20-62%)
Total active (including metabolites)				↓ 68% (55-78%)	↓ 60% (52-68%)	NA[j]
Carbamazepine	200 mg qd × 3 days, 200 mg bid × 3 days, then 400 mg qd × 29 days	600 mg qd × 14 days	12	↓ 20% (15-24%)	↓ 27% (20-33%)	↓ 35% (24-44%)
Epoxide metabolite				↔	↔	↓ 13% (↓ 30-↑ 7%)
Cetirizine	10 mg single dose	600 mg qd × 10 days	11	↓ 24% (18-30%)	↔	NA
Diltiazem	240 mg × 21 days	600 mg qd × 14 days	13	↓ 60% (50-68%)	↓ 69% (55-79%)	↓ 63% (44-75%)
Desacetyl diltiazem				↓ 64% (57-69%)	↓ 75% (59-84%)	↓ 62% (44-75%)
N-monodes-methyl diltiazem				↓ 28% (7-44%)	↓ 37% (17-52%)	↓ 37% (17-52%)
Ethinyl estradiol/ Norgestimate	0.035 mg/0.25 mg × 14 days	600 mg qd × 14 days				
Ethinyl estradiol			21	↔	↔	↔
Norelgestromin			21	↓ 46% (39-52%)	↓ 64% (62-67%)	↓ 82% (79-85%)

Reference ID: 3512480

Table 7: Effect of Efavirenz on Coadministered Drug Plasma C_{max}, AUC, and C_{min}

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Coadministered Drug (mean % change) C_{max} (90% CI)	AUC (90% CI)	C_{min} (90% CI)
Levonorgestrel			6	↓ 80% (77-83%)	↓ 83% (79-87%)	↓ 86% (80-90%)
Lorazepam	2 mg single dose	600 mg qd × 10 days	12	↑ 16% (2-32%)	↔	NA
Methadone	Stable maintenance 35-100 mg daily	600 mg qd × 14-21 days	11	↓ 45% (25-59%)	↓ 52% (33-66%)	NA
Bupropion	150 mg single dose (sustained-release)	600 mg qd × 14 days	13	↓ 34% (21-47%)	↓ 55% (48-62%)	NA
Hydroxy-bupropion				↑ 50% (20-80%)	↔	NA
Paroxetine	20 mg qd × 14 days	600 mg qd × 14 days	16	↔	↔	↔
Sertraline	50 mg qd × 14 days	600 mg qd × 14 days	13	↓ 29% (15-40%)	↓ 39% (27-50%)	↓ 46% (31-58%)

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

[a] Compared with atazanavir 400 mg qd alone.

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

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

[d] Values are for lopinavir; the pharmacokinetics of ritonavir in this study were unaffected by concurrent efavirenz.

[e] 95% CI.

[f] Soft Gelatin Capsule.

[g] Tenofovir disoproxil fumarate.

[h] 90% CI not available.

[i] Relative to steady-state administration of voriconazole (400 mg for 1 day, then 200 mg po q12h for 2 days).

[j] Not available because of insufficient data.

NA = not available.

Table 8: Effect of Coadministered Drug on Efavirenz Plasma C_{max}, AUC, and C_{min}

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Efavirenz (mean % change) C_{max} (90% CI)	AUC (90% CI)	C_{min} (90% CI)
Indinavir	800 mg q8h × 14 days	200 mg qd × 14 days	11	↔	↔	↔
Lopinavir/ritonavir	400/100 mg q12h × 9 days	600 mg qd × 9 days	11,12[a]	↔	↓ 16% (↓ 38-↑ 15%)	↓ 16% (↓ 42-↑ 20%)
Nelfinavir	750 mg q8h × 7 days	600 mg qd × 7 days	10	↓ 12% (↓ 32-↑ 13%)[b]	↓ 12% (↓ 35-↑ 18%)[b]	↓ 21% (↓ 53-↑ 33%)
Ritonavir	500 mg q12h × 8 days	600 mg qd × 10 days	9	↑ 14% (4-26%)	↑ 21% (10-34%)	↑ 25% (7-46%)[b]
Saquinavir SGC[c]	1200 mg q8h × 10 days	600 mg qd × 10 days	13	↓ 13% (5-20%)	↓ 12% (4-19%)	↓ 14% (2-24%)[b]

Reference ID: 3512480

Table 8: Effect of Coadministered Drug on Efavirenz Plasma C_{max}, AUC, and C_{min}

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Efavirenz (mean % change) C_{max} (90% CI)	Efavirenz (mean % change) AUC (90% CI)	Efavirenz (mean % change) C_{min} (90% CI)
Tenofovir[d]	300 mg qd	600 mg qd × 14 days	30	↔	↔	↔
Boceprevir	800 mg tid × 6 days	600 mg qd × 16 days	NA	↑ 11% (2-20%)	↑ 20% (15-26%)	NA
Telaprevir	750 mg q8h × 10 days	600 mg qd × 20 days	21	↓ 16% (7-24%)	↓ 7% (2-13%)	↓ 2% (↓ 6-↑ 2%)
Telaprevir, coadministered with tenofovir disoproxil fumarate (TDF)	1125 mg q8h × 7 days	600 mg efavirenz /300 mg TDF qd × 7 days	15	↓ 24% (15-32%)	↓ 18% (10-26%)	↓ 10% (↓ 19-↑ 1%)
	1500 mg q12h × 7 days	600 mg efavirenz /300 mg TDF qd × 7 days	16	↓ 20% (14-26%)	↓ 15% (9-21%)	↓ 11% (4-18%)
Azithromycin	600 mg single dose	400 mg qd × 7 days	14	↔	↔	↔
Clarithromycin	500 mg q12h × 7 days	400 mg qd × 7 days	12	↑ 11% (3-19%)	↔	↔
Fluconazole	200 mg × 7 days	400 mg qd × 7 days	10	↔	↑ 16% (6-26%)	↑ 22% (5-41%)
Itraconazole	200 mg q12h × 14 days	600 mg qd × 28 days	16	↔	↔	↔
Rifabutin	300 mg qd × 14 days	600 mg qd × 14 days	11	↔	↔	↓ 12% (↓ 24-↑ 1%)
Rifampin	600 mg × 7 days	600 mg qd × 7 days	12	↓ 20% (11-28%)	↓ 26% (15-36%)	↓ 32% (15-46%)
Voriconazole	400 mg po q12h × 1 day, then 200 mg po q12h × 8 days	400 mg qd × 9 days	NA	↑ 38%[e]	↑ 44%[e]	NA
	300 mg po q12h days 2-7	300 mg qd × 7 days	NA	↓ 14%[f] (7-21%)	↔[f]	NA
	400 mg po q12h days 2-7	300 mg qd × 7 days	NA	↔[f]	↑ 17%[f] (6-29%)	NA
Artemether/ Lumefantrine	Artemether 20 mg/ lumefantrine 120 mg tablets (6 4-tablet doses over 3 days)	600 mg qd × 26 days	12	↔	↓ 17%	NA
Atorvastatin	10 mg qd × 4 days	600 mg qd × 15 days	14	↔	↔	↔
Pravastatin	40 mg qd × 4 days	600 mg qd × 15 days	11	↔	↔	↔
Simvastatin	40 mg qd × 4 days	600 mg qd × 15 days	14	↓ 12% (↓ 28-↑ 8%)	↔	↓ 12% (↓ 25-↑ 3%)
Aluminum hydroxide 400 mg, magnesium hydroxide 400 mg, plus simethicone 40 mg	30 mL single dose	400 mg single dose	17	↔	↔	NA
Carbamazepine	200 mg qd × 3 days, 200 mg bid × 3 days, then	600 mg qd × 35 days	14	↓ 21% (15-26%)	↓ 36% (32-40%)	↓ 47% (41-53%)

Table 8: Effect of Coadministered Drug on Efavirenz Plasma C_{max}, AUC, and C_{min}

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Efavirenz (mean % change) C_{max} (90% CI)	Efavirenz (mean % change) AUC (90% CI)	Efavirenz (mean % change) C_{min} (90% CI)
	400 mg qd × 15 days					
Cetirizine	10 mg single dose	600 mg qd × 10 days	11	↔	↔	↔
Diltiazem	240 mg × 14 days	600 mg qd × 28 days	12	↑ 16% (6-26%)	↑ 11% (5-18%)	↑ 13% (1-26%)
Famotidine	40 mg single dose	400 mg single dose	17	↔	↔	NA
Paroxetine	20 mg qd × 14 days	600 mg qd × 14 days	12	↔	↔	↔
Sertraline	50 mg qd × 14 days	600 mg qd × 14 days	13	↑ 11% (6-16%)	↔	↔

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

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

[b] 95% CI.

[c] Soft Gelatin Capsule.

[d] Tenofovir disoproxil fumarate.

[e] 90% CI not available.

[f] Relative to steady-state administration of efavirenz (600 mg once daily for 9 days).

NA = not available.

12.4 Microbiology

Mechanism of Action

Efavirenz is an NNRTI of HIV-1. Efavirenz activity is mediated predominantly by noncompetitive inhibition of HIV-1 reverse transcriptase. HIV-2 reverse transcriptase and human cellular DNA polymerases α, β, γ, and δ are not inhibited by efavirenz.

Reference ID: 3512480

Antiviral Activity in Cell Culture

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

Resistance

In cell culture

In cell culture, HIV-1 isolates with reduced susceptibility to efavirenz (>380-fold increase in EC_{90} value) emerged rapidly in the presence of drug. Genotypic characterization of these viruses identified single amino acid substitutions L100I or V179D, double substitutions L100I/V108I, and triple substitutions L100I/V179D/Y181C in reverse transcriptase.

Clinical studies

Clinical isolates with reduced susceptibility in cell culture to efavirenz have been obtained. One or more substitutions at amino acid positions 98, 100, 101, 103, 106, 108, 188, 190, 225, and 227 in reverse transcriptase were observed in patients failing treatment with efavirenz in combination with indinavir, or with zidovudine plus lamivudine. The K103N substitution was the most frequently observed. Long-term resistance surveillance (average 52 weeks, range 4-106

Reference ID: 3512480

weeks) analyzed 28 matching baseline and virologic failure isolates. Sixty-one percent (17/28) of these failure isolates had decreased efavirenz susceptibility in cell culture with a median 88-fold change in efavirenz susceptibility (EC_{50} value) from reference. The most frequent NNRTI substitution to develop in these patient isolates was K103N (54%). Other NNRTI substitutions that developed included L100I (7%), K101E/Q/R (14%), V108I (11%), G190S/T/A (7%), P225H (18%), and M230I/L (11%).

Cross-Resistance

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term carcinogenicity studies in mice and rats were carried out with efavirenz. Mice were dosed with 0, 25, 75, 150, or 300 mg/kg/day for 2 years. Incidences of hepatocellular adenomas and carcinomas and pulmonary alveolar/bronchiolar adenomas were increased above background in females. No increases in tumor incidence above background were seen in males. There was no NOAEL in females established for this study because tumor findings occurred at all doses. AUC at the NOAEL (150 mg/kg) in the males was approximately 0.9 times that in humans at the recommended clinical dose. In the rat study, no increases in tumor incidence were observed at doses up to 100 mg/kg/day, for which AUCs were 0.1 (males) or 0.2 (females) times those in humans at the recommended clinical dose.

Mutagenesis

Efavirenz tested negative in a battery of *in vitro* and *in vivo* genotoxicity assays. These included bacterial mutation assays in *S. typhimurium* and *E. coli*, mammalian mutation assays in Chinese hamster ovary cells, chromosome aberration assays in human peripheral blood lymphocytes or Chinese hamster ovary cells, and an *in vivo* mouse bone marrow micronucleus assay.

Impairment of Fertility

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. The AUCs at the NOAEL values in male (200 mg/kg) and female (100 mg/kg) rats were approximately ≤0.15 times that in humans at the recommended clinical dose.

13.2 Animal Toxicology

Nonsustained convulsions were observed in 6 of 20 monkeys receiving efavirenz at doses yielding plasma AUC values 4- to 13-fold greater than those in humans given the recommended dose [*see Warnings and Precautions (5.9)*].

14 CLINICAL STUDIES

14.1 Adults

Study 006, a randomized, open-label trial, compared SUSTIVA (600 mg once daily) + zidovudine (ZDV, 300 mg q12h) + lamivudine (LAM, 150 mg q12h) or SUSTIVA (600 mg once daily) + indinavir (IDV, 1000 mg q8h) with indinavir (800 mg q8h) + zidovudine (300 mg q12h) + lamivudine (150 mg q12h). Twelve hundred sixty-six patients (mean age 36.5 years [range 18-81], 60% Caucasian, 83% male) were enrolled. All patients were efavirenz-, lamivudine-, NNRTI-, and PI-naive at study entry. The median baseline CD4+ cell count was 320 cells/mm^3 and the median baseline HIV-1 RNA level was 4.8 $\log_{10}$ copies/mL. Treatment outcomes with standard assay (assay limit 400 copies/mL) through 48 and 168 weeks are shown in Table 9. Plasma HIV RNA levels were quantified with standard (assay limit 400 copies/mL) and ultrasensitive (assay limit 50

Reference ID: 3512480