HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use efavirenz safely and effectively. See full prescribing information for efavirenz.

Efavirenz tablets

Initial U.S. Approval: 1998

-- **RECENT MAJOR CHANGES** --

Warnings and Precautions, Reproductive Risk Potential (5.6) 3/2009

-- **INDICATIONS AND USAGE** --

Efavirenz is a non-nucleoside reverse transcriptase inhibitor indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 infection. (1)

-- **DOSAGE AND ADMINISTRATION** --

- Efavirenz should be taken orally once daily on an empty stomach, preferably at bedtime. (2)
- Recommended adult dose: 600 mg. (2.1)
- With voriconazole, increase voriconazole maintenance dose to 400 mg every 12 hours and decrease efavirenz dose to 300 mg once daily using the tablet formulation. (2.1)

Pediatric Patients at Least 3 Years, at Least 10 kg, and Who Are Able to Swallow Tablets (2.2)					
kg	**Lbs**	**dose**	**kg**	**lbs**	**Dose**
10-<15	22-<33	200 mg (1 tab)	25-<32.5	55-<71.5	350 mg (1.75 tabs)
15-<20	33-<44	250 mg (1.25 tabs)	32.5-<40	71.5-<88	400 mg (2 tabs)
20-<25	44-<55	300 mg (1.5 tabs)	At least 40	At least 88	600 mg (3 tabs)

-- **DOSAGE FORMS AND STRENGTHS** --

Tablets: Cross Scored 200 mg. (3)

-- **CONTRAINDICATIONS** --

- Efavirenz is contraindicated in patients with previously demonstrated hypersensitivity (eg, Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the components of this product. (4.1)
- For some drugs, competition for CYP3A by efavirenz could result in inhibition of their metabolism and create the potential for serious and/or life-threatening adverse reactions (eg, cardiac arrhythmias, prolonged sedation, or respiratory depression). (4.2)

-- **WARNINGS AND PRECAUTIONS** --

- *Do not use as a single agent* or add on as a sole agent to a failing regimen. Consider potential for cross resistance when choosing other agents. (5.2)
- Not recommended with ATRIPLA (efavirenz, emtricitabine, and tenofovir disoproxil fumarate) and SUSTIVA (efavirenz). (5.3)
- *Serious psychiatric symptoms:* Immediate medical evaluation is recommended for serious psychiatric symptoms such as severe depression or suicidal ideation. (5.4, 17.5)
- *Nervous system symptoms* (NSS): NSS are frequent, usually begin 1-2 days after initiating therapy and resolve in 2-4 weeks. Dosing at bedtime may improve tolerability. NSS are not predictive of onset of psychiatric symptoms. (5.5, 6.1, 17.4)
- *Pregnancy:* Fetal harm can occur when administered to a pregnant woman during the first trimester. Women should be apprised of the potential harm to the fetus. (17.7)
- *Hepatotoxicity:* Monitor liver function tests before and during treatment in patients with underlying hepatic disease, including hepatitis B and C, or marked transaminase elevations. (5.8, 8.6)
- *Rash:* Rash usually begins within 1-2 weeks after initiating therapy and resolves within 4 weeks. Discontinue if severe rash develops. (5.7, 6.1, 17.6)
- *Convulsions:* Use caution in patients with a history of seizures. (5.9)
- *Lipids:* Total cholesterol and triglyceride elevations. Monitor before therapy and periodically thereafter. (5.10)
- *Immune reconstitution syndrome:* May necessitate further evaluation and treatment. (5.11)
- *Redistribution/accumulation of body fat:* Observed in patients receiving antiretroviral therapy. (5.12, 17.8)

-- **ADVERSE REACTIONS** --

Most common adverse reactions (>5%, moderate-severe) are rash, dizziness, nausea, headache, fatigue, insomnia, and vomiting. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Strides Inc. at (732)-839-1601 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

-- **DRUG INTERACTIONS** --

Coadministration of efavirenz can alter the concentrations of other drugs and other drugs may alter the concentrations of efavirenz. The potential for drug-drug interactions must be considered before and during therapy. (4.2, 7.1, 12.3)

-- **USE IN SPECIFIC POPULATIONS** --

- *Pregnancy:* Women should avoid pregnancy during efavirenz therapy and for 12 weeks after discontinuation. (5.6)
- *Nursing mothers:* Women infected with HIV should be instructed not to breast-feed. (8.3)
- *Hepatitis B or C coinfection or therapy with medications associated with liver toxicity:* Use caution in patients with hepatic impairment. (5.8, 6.1, 8.6)
- *Pediatric patients:* The incidence of rash was higher than in adults. (5.7, 6.1, 6.2, 8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling **Revised: 02/2010**

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Efavirenz in combination with other antiretroviral agents is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection. This indication is based on two clinical trials of at least one year duration that demonstrated prolonged suppression of HIV RNA [see *Clinical Studies (14)*].

2 DOSAGE AND ADMINISTRATION

2.1 Adults

The recommended dosage of efavirenz is 600 mg orally, once daily, in combination with a protease inhibitor and/or nucleoside analogue reverse transcriptase inhibitors (NRTIs). It is recommended that efavirenz be taken on an empty stomach, preferably at bedtime. The increased efavirenz concentrations observed following administration of efavirenz with food may lead to an increase in frequency of adverse reactions [see *Clinical Pharmacology (12.3)*]. Dosing at bedtime may improve the tolerability of nervous system symptoms [see *Warnings and Precautions (5.5), Adverse Reactions (6.1)*, and *Patient Counseling Information (17.4)*].

Concomitant Antiretroviral Therapy

Efavirenz must be given in combination with other antiretroviral medications [see *Indications and Usage (1), Warnings and Precautions (5.2), Drug Interactions (7.1)*, and *Clinical Pharmacology (12.3)*].

Dosage Adjustment

If efavirenz is coadministered with voriconazole, the voriconazole maintenance dose should be increased to 400 mg every 12 hours and the efavirenz dose should be decreased to 300 mg once daily (one 200-mg tablet plus one half of 200-mg tablet). See *Drug Interactions (7.1, Table 7)* and *Clinical Pharmacology (12.3, Tables 8* and *9)*.

2.2 Pediatric Patients

It is recommended that efavirenz be taken on an empty stomach, preferably at bedtime. Table 1 describes the recommended dose of efavirenz for pediatric patients 3 years of age or older, weighing between 10 and 40 kg, and who are able to swallow tablets [see *Use in Specific Populations (8.4)*]. The recommended dosage of efavirenz for pediatric patients weighing greater than 40 kg is 600 mg once daily.

Table 1: Pediatric Dose to be Administered Once Daily

Body Weight: Kg	Body Weight: lbs	Efavirenz (EFV) Dose (mg)	Total Number of Tablets Using EFV Cross Scored 200 mg Tablets[a]
10 to less than 15	22 to less than 33	200	1 tablet
15 to less than 20	33 to less than 44	250	1.25 tablet
20 to less than 25	44 to less than 55	300	1.50 tablets
25 to less than 32.5	55 to less than 71.5	350	1.75 tablets
32.5 to less than 40	71.5 to less than 88	400	2 tablets
at least 40	at least 88	600	3 tablets

[a] If a tablet needs to be split, rest the tablet on a flat surface with the cross score lines facing up, and using fingers press down on opposite edges at the same time.

3 DOSAGE FORMS AND STRENGTHS

Evavirenz Tablets, 200-mg are cross scored off-white colored, circular, biconvex, film coated tablets with cross score line on one side and plain on other side.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Efavirenz is contraindicated in patients with previously demonstrated clinically significant hypersensitivity (eg, Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the components of this product.

4.2 Contraindicated Drugs

For some drugs, competition for CYP3A by efavirenz could result in inhibition of their metabolism and create the potential for serious and/or life-threatening adverse reactions (eg, cardiac arrhythmias, prolonged sedation, or respiratory depression). Drugs that are contraindicated with efavirenz are listed in Table 2.

Table 2: Drugs That Are Contraindicated or Not Recommended for Use With Efavirenz

Drug Class: Drug Name	Clinical Comment
Antimigraine: ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine)	Potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
Benzodiazepines: midazolam, triazolam	Potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.
Calcium channel blocker: bepridil	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
GI motility agent: cisapride	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Neuroleptic: pimozide	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
St. John's wort *(Hypericum perforatum)*	May lead to loss of virologic response and possible resistance to efavirenz or to the class of non-nucleoside reverse transcriptase inhibitors (NNRTI).

5 WARNINGS AND PRECAUTIONS

5.1 Drug Interactions

Efavirenz plasma concentrations may be altered by substrates, inhibitors, or inducers of CYP3A. Likewise, efavirenz may alter plasma concentrations of drugs metabolized by CYP3A [see *Contraindications (4.2)* and *Drug Interactions (7.1)*].

5.2 Resistance

Efavirenz must not be used as a single agent to treat HIV-1 infection or added on as a sole agent to a failing regimen. 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.

5.3 Coadministration with Related Products

Coadministration of efavirenz with ATRIPLA (efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) and SUSTIVA (efavirenz) capsules and tablets is not recommended, since efavirenz is one of their active ingredients.

5.4 Psychiatric Symptoms

Serious psychiatric adverse experiences have been reported in patients treated with efavirenz. In controlled trials of 1008 patients treated with regimens containing efavirenz for a mean of 2.1 years and 635 patients treated with control regimens for a mean of 1.5 years, the frequency (regardless of causality) of specific serious psychiatric events among patients who received efavirenz or control regimens, respectively, were severe depression (2.4%, 0.9%), suicidal ideation (0.7%, 0.3%), nonfatal suicide attempts (0.5%, 0), aggressive behavior (0.4%, 0.5%), paranoid reactions (0.4%, 0.3%), and manic reactions (0.2%, 0.3%). When psychiatric symptoms similar to those noted above were combined and evaluated as a group in a multifactorial analysis of data from Study 006, treatment with efavirenz was associated with an increase in the occurrence of these selected psychiatric symptoms. Other factors associated with an increase in the occurrence of these psychiatric symptoms were history of injection drug use, psychiatric history, and receipt of psychiatric medication at study entry; similar associations were observed in both the efavirenz and control treatment groups. In Study 006, onset of new serious psychiatric symptoms occurred throughout the study for both efavirenz-treated and control-treated patients. One percent of efavirenz-treated patients discontinued or interrupted treatment because of one or more of these selected psychiatric symptoms. There have also been occasional postmarketing reports of death by suicide, delusions, and psychosis-like behavior, although a causal relationship to the use of efavirenz 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 efavirenz, and if so, to determine whether the risks of continued therapy outweigh the benefits. See *Adverse Reactions (6.1)*.

5.5 Nervous System Symptoms

Fifty-three percent (531/1008) of patients receiving efavirenz in controlled trials reported central nervous system symptoms (any grade, regardless of causality) compared to 25% (156/635) of patients receiving control regimens [see *Adverse Reactions (6.1, Table 4)*]. These symptoms included, but were not limited to, dizziness (28.1% of the 1008 patients), insomnia (16.3%), impaired concentration (8.3%), somnolence (7.0%), abnormal dreams (6.2%), and hallucinations (1.2%). These symptoms were severe in 2.0% of patients, and 2.1% of patients discontinued therapy as a result. These symptoms usually begin during the first or second day of therapy and generally resolve after the first 2-4 weeks of therapy. After 4 weeks of therapy, the prevalence of nervous system symptoms of at least moderate severity ranged from 5% to 9% in patients treated with regimens containing efavirenz and from 3% to 5% in patients treated with a control regimen. Patients should be informed that these common symptoms were likely to improve with continued therapy and were not predictive of subsequent onset of the less frequent psychiatric symptoms [see *Warnings and Precautions (5.4)*]. Dosing at bedtime may improve the tolerability of these nervous system symptoms [see *Dosage and Administration (2)*].

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

Patients receiving efavirenz should be alerted to the potential for additive central nervous system effects when efavirenz 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.

5.6 Reproductive Risk Potential

Pregnancy Category D. Efavirenz may cause fetal harm when administered during the first trimester to a pregnant woman. Pregnancy should be avoided in women receiving efavirenz. Barrier contraception must always be used in combination with other methods of contraception (eg, oral or other hormonal contraceptives). Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of efavirenz is recommended. Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz. If this drug is used during the first trimester of pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus.

There are no adequate and well-controlled studies in pregnant women. 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.

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

5.7 Rash

In controlled clinical trials, 26% (266/1008) of patients treated with 600 mg efavirenz experienced new-onset skin rash compared with 17% (111/635) of patients treated in control groups [see *Adverse Reactions (6.1, Table 5)*]. Rash associated with blistering, moist desquamation, or ulceration occurred in 0.9% (9/1008) of patients treated with efavirenz. The incidence of Grade 4 rash (e.g., erythema multiforme, Stevens-Johnson syndrome) in patients treated with efavirenz in all studies and expanded access was 0.1%. Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first 2 weeks of initiating therapy with efavirenz (median time to onset of rash in adults was 11 days) and, in most patients continuing therapy with efavirenz, rash resolves within 1 month (median duration, 16 days). The discontinuation rate for rash in clinical trials was 1.7% (17/1008). Efavirenz can be reinitiated in patients interrupting therapy because of rash. Efavirenz should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement, or fever. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash.

Rash was reported in 26 of 57 pediatric patients (46%) treated with efavirenz capsules [see *Adverse Reactions (6.1, 6.2)*]. One pediatric patient experienced Grade 3 rash (confluent rash with fever), and two patients had Grade 4 rash (erythema multiforme). The median time to onset of rash in pediatric patients was 8 days. Prophylaxis with appropriate antihistamines before initiating therapy with efavirenz in pediatric patients should be considered.

5.8 Liver Enzymes

In patients with known or suspected history of hepatitis B or C infection and in patients treated with other medications associated with liver toxicity, monitoring of liver enzymes is recommended. In patients with persistent elevations of serum transaminases to greater than five times the upper limit of the normal range, the benefit of continued therapy with efavirenz needs to be weighed against the unknown risks of significant liver toxicity [see *Adverse Reactions (6.1)* and *Use in Specific Populations (8.6)*].

5.9 Convulsions

Convulsions have been observed in patients receiving efavirenz, generally in the presence of known medical history of seizures [see *Nonclinical Toxicology (13.2)*]. Caution must be taken in any patient with a history of seizures. Patients who are receiving concomitant anticonvulsant medications primarily metabolized by the liver, such as phenytoin and phenobarbital, may require periodic monitoring of plasma levels [see *Drug Interactions (7.1)*].

5.10 Lipid Evaluations

Treatment with efavirenz has resulted in increases in the concentration of total cholesterol and triglycerides [see *Adverse Reactions (6.1)*]. Cholesterol and triglyceride testing should be performed before initiating efavirenz therapy and at periodic intervals during therapy.

5.11 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including efavirenz. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections [such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jiroveci* pneumonia (PCP), or tuberculosis], which may necessitate further evaluation and treatment.

5.12 Fat Redistribution

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

6 ADVERSE REACTIONS

The most significant adverse reactions observed in patients treated with efavirenz are:

- psychiatric symptoms [see *Warnings and Precautions (5.4)*],
- nervous system symptoms [see *Warnings and Precautions (5.5)*],
- rash [see *Warnings and Precautions (5.7)*].

The most common (>5% in either efavirenz treatment group) adverse reactions of at least moderate severity among patients in Study 006 treated with efavirenz in combination with zidovudine/lamivudine or indinavir were rash, dizziness, nausea, headache, fatigue, insomnia, and vomiting.

6.1 Clinical Trials Experience in Adults

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.
Selected clinical adverse reactions of moderate or severe intensity observed in ≥2% of efavirenz-treated patients in two controlled clinical trials are presented in Table 3.

Table 3: Selected Treatment-Emergent[a] Adverse Reactions of Moderate or Severe Intensity Reported in ≥2% of Efavirenz-Treated Patients in Studies 006 and ACTG 364

Adverse Reactions	Study 006 LAM-, NNRTI-, and Protease Inhibitor-Naive Patients			Study ACTG 364 NRTI-experienced, NNRTI- and Protease Inhibitor-Naive Patients		
	Efavirenz[b] + ZDV/LAM (n=412) 180 weeks[c]	Efavirenz[b] + Indinavir (n=415) 102 weeks[c]	Indinavir + ZDV/LAM (n=401) 76 weeks[c]	Efavirenz[b] + Nelfinavir + NRTIs (n=64) 71.1 weeks[c]	Efavirenz[b] + NRTIs (n=65) 70.9 weeks[c]	Nelfinavir + NRTIs (n=66) 62.7 weeks[c]
Body as a Whole						
Fatigue	8%	5%	9%	0	2%	3%
Pain	1%	2%	8%	13%	6%	17%
Central and Peripheral Nervous System						
Dizziness	9%	9%	2%	2%	6%	6%
Headache	8%	5%	3%	5%	2%	3%
Insomnia	7%	7%	2%	0	0	2%
Concentration impaired	5%	3%	<1%	0	0	0
Abnormal dreams	3%	1%	0	—	—	—
Somnolence	2%	2%	<1%	0	0	0
Anorexia	1%	<1%	<1%	0	2%	2%
Gastrointestinal						
Nausea	10%	6%	24%	3%	2%	2%
Vomiting	6%	3%	14%	—	—	—
Diarrhea	3%	5%	6%	14%	3%	9%
Dyspepsia	4%	4%	6%	0	0	2%
Abdominal pain	2%	2%	5%	3%	3%	3%
Psychiatric						
Anxiety	2%	4%	<1%	—	—	—
Depression	5%	4%	<1%	3%	0	5%
Nervousness	2%	2%	0	2%	0	2%
Skin & Appendages						
Rash[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] Efavirenz 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 efavirenz and 635 patients treated with a control regimen in controlled trials, Table 4 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 3.

Table 4: Percent of Patients with One or More Selected Nervous System Symptoms[a,b]

Percent of Patients with:	Efavirenz 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 efavirenz. In controlled trials, psychiatric symptoms observed at a frequency of >2% among patients treated with efavirenz or control regimens, respectively, were depression (19%, 16%), anxiety (13%, 9%), and nervousness (7%, 2%).

Rash

For 1008 adults and 57 pediatric patients treated with regimens containing efavirenz and 635 patients treated with a control regimen in controlled trials, the frequency of rash by NCI grade and the discontinuation rates as a result of rash in clinical studies are provided in Table 5 [see *Warnings and Precautions (5.7)*].

Table 5: Percent of Patients with Treatment-Emergent Rash[a,b]

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

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

As seen in Table 5, rash is more common in pediatric patients and more often of higher grade (i.e., more severe) [see *Warnings and Precautions (5.7)*].

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

Laboratory Abnormalities

Selected Grade 3-4 laboratory abnormalities reported in ≥2% of efavirenz-treated patients in two clinical trials are presented in Table 6.

Table 6: Selected Grade 3-4 Laboratory Abnormalities Reported in ≥2% of Efavirenz-Treated Patients in Studies 006 and ACTG 364

Variable	Limit	Study 006 LAM-, NNRTI-, and Protease Inhibitor-Naive Patients			Study ACTG 364 NRTI-experienced, NNRTI- and Protease Inhibitor-Naive Patients		
		Efavirenz[a] + ZDV/LAM (n=412) 180 weeks[b]	Efavirenz[a] + Indinavir (n=415) 102 weeks[b]	Indinavir + ZDV/LAM (n=401) 76 weeks[b]	Efavirenz[a] + Nelfinavir + NRTIs (n=64) 71.1 weeks[b]	Efavirenz[a] + NRTIs (n=65) 70.9 weeks[b]	Nelfinavir + NRTIs (n=66) 62.7 weeks[b]
Chemistry							
ALT	>5 x ULN	5%	8%	5%	2%	6%	3%
AST	>5 x ULN	5%	6%	5%	6%	8%	8%
GGT[c]	>5 x ULN	8%	7%	3%	5%	0	5%
Amylase	>2 x ULN	4%	4%	1%	0	6%	2%
Glucose	>250 mg/dL	3%	3%	3%	5%	2%	3%
Triglycerides[d]	≥751 mg/dL	9%	6%	6%	11%	8%	17%
Hematology							
Neutrophils	<750/mm³	10%	3%	5%	2%	3%	2%

[a] Efavirenz provided as 600 mg once daily.
[b] Median duration of treatment.
[c] Isolated elevations of GGT in patients receiving efavirenz 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 efavirenz-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 efavirenz 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 efavirenz arms and 7% of patients in the control arm. Among coinfected patients, 3% of those treated with efavirenz-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 efavirenz. In patients treated with efavirenz + zidovudine + lamivudine, increases from baseline in nonfasting total cholesterol and HDL of approximately 20% and 25%, respectively, were observed. In patients treated with efavirenz + 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 efavirenz + zidovudine + lamivudine; 54% and 20%, respectively, of patients treated with efavirenz + indinavir; and 28% and 4%, respectively, of patients treated with indinavir + zidovudine + lamivudine. The effects of efavirenz 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

Clinical adverse experiences observed in ≥10% of 57 pediatric patients aged 3 to 16 years who received efavirenz capsules, nelfinavir, and one or more NRTIs in Study ACTG 382 [see *Use In Specific Populations (8.4)*] were rash (46%), diarrhea/loose stools (39%), fever (21%), cough (16%), dizziness/lightheaded/fainting (16%), ache/pain/discomfort (14%), nausea/vomiting (12%), and headache (11%). The incidence of nervous system symptoms was 18% (10/57). One patient experienced Grade 3 rash, two patients had Grade 4 rash, and five patients (9%) discontinued because of rash [see *Warnings and Precautions (5.7)* and *Adverse Reactions (6.1, Table 5)*].

6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of efavirenz. 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

Endocrine: gynecomastia

Gastrointestinal: constipation, malabsorption

Cardiovascular: flushing, palpitations

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

Metabolic and Nutritional: hypercholesterolemia, hypertriglyceridemia

Musculoskeletal: arthralgia, myalgia, myopathy

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

Respiratory: dyspnea

Skin and Appendages: erythema multiforme, 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. Other compounds that are substrates of CYP3A may have decreased plasma concentrations when coadministered with efavirenz. *In vitro* studies have demonstrated that efavirenz inhibits CYP2C9, 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 that induce CYP3A activity (e.g., phenobarbital, rifampin, rifabutin) would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations. Drug interactions with efavirenz are summarized in Tables 2 and 7 [for pharmacokinetics data see *Clinical Pharmacology (12.3, Tables 8 and 9)*]. The tables include potentially significant interactions, but are not all inclusive.

Table 7: Established[a] and Other Potentially Significant[b] Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug name	Effect	Clinical Comment
Antiretroviral 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 efavirenz is administered with fosamprenavir/ritonavir once daily. No change in the ritonavir dose is required when efavirenz is administered with fosamprenavir plus ritonavir twice daily.
Protease inhibitor: Atazanavir	↓ atazanavir[a]	*Treatment-naive patients:* When coadministered with efavirenz, the recommended dose of atazanavir is 400 mg with ritonavir 100 mg (together once daily with food) and efavirenz 600 mg (once daily on an empty stomach, preferably at bedtime). *Treatment-experience patients:* Coadministration of efavirenz and atazanavir is not recommended.
Protease inhibitor: Indinavir	↓ indinavir[a]	The optimal dose of indinavir, when given in combination with efavirenz, is not known. Increasing the indinavir dose to 1000 mg every 8 hours does not compensate for the increased indinavir metabolism due to efavirenz. When indinavir at an increased dose (1000 mg every 8 hours) was given with efavirenz (600 mg once daily), the indinavir AUC and C_{min} were decreased on average by 33-46% and 39-57%, respectively, compared to when indinavir (800 mg every 8 hours) was given alone.
Protease inhibitor: Lopinavir/ritonavir	↓ lopinavir[a]	Lopinavir/ritonavir tablets should not be administered once-daily in combination with efavirenz. In antiretroviral-naive patients, lopinavir/ritonavir tablets can be used twice daily in combination with efavirenz with no dose adjustment. A dose increase of lopinavir/ritonavir tablets to 600/150 mg (3 tablets) twice daily may be considered when used in combination with efavirenz in treatment-experienced patients where decreased susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). A dose increase of lopinavir/ritonavir to 533/133 mg (4 capsules or 6.5 mL) twice daily taken with food is recommended when used in combination with efavirenz.
Protease inhibitor: Ritonavir	↑ ritonavir[a] ↑ efavirenz[a]	When ritonavir 500 mg q12h was coadministered with efavirenz 600 mg once daily, 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 efavirenz is used in combination with ritonavir.
Protease inhibitor: Saquinavir	↓ saquinavir[a]	Should not be used as sole protease inhibitor in combination with efavirenz.
Other agents		
Anticoagulants: Warfarin	↓ or ↑ warfarin	Plasma concentrations and effects potentially increased or decreased by efavirenz.
Anticonvulsants: Carbamazepine	↓ carbamazepine[a] ↓ efavirenz[a]	There are insufficient data to make a dose recommendation for efavirenz. Alternative anticonvulsant treatment should be used.
Phenytoin Phenobarbital	↓ anticonvulsant ↓ efavirenz	Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.
Antidepressant: Sertraline	↓ sertraline[a]	Increases in sertraline dosage should be guided by clinical response.
Antifungals: Voriconazole	↓ voriconazole[a] ↑ efavirenz[a]	Efavirenz 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 efavirenz-associated side effects. When voriconazole is coadministered with efavirenz, voriconazole maintenance dose should be increased to 400 mg every 12 hours and efavirenz dose should be decreased to 300 mg once daily using the tablet formulation. [See *Dosage and Administration* (2.1) and *Clinical Pharmacology* (12.3, *Tables* 8 and 9).]
Itraconazole	↓ itraconazole[a] ↓ hydroxyitraconazole[a]	Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered.
Ketoconazole	↓ ketoconazole	Drug interaction studies with efavirenz and ketoconazole have not been conducted. Efavirenz has the potential to decrease plasma concentrations of ketoconazole.
Anti-infective: Clarithromycin	↓ clarithromycin[a] ↑ 14-OH metabolite[a]	Plasma concentrations decreased by efavirenz; clinical significance unknown. In uninfected volunteers, 46% developed rash while receiving efavirenz and clarithromycin. No dose adjustment of efavirenz 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 efavirenz.
Antimycobacterial: Rifabutin	↓ rifabutin[a]	Increase daily dose of rifabutin by 50%. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week.
Rifampin	↓ efavirenz[a]	Clinical significance of reduced efavirenz concentrations is unknown. Dosing recommendations for concomitant use of efavirenz and rifampin have not been established.
Calcium channel blockers: Diltiazem	↓ diltiazem[a] ↓ desacetyl diltiazem[a] ↓ N-monodesmethyl diltiazem[a]	Diltiazem dose adjustments should be guided by clinical response (refer to the complete prescribing information for diltiazem). No dose adjustment of efavirenz is necessary when administered with diltiazem.
Others (e.g., 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 the CYP3A enzyme. The potential exists for reduction in plasma concentrations of the calcium channel blocker. Dose adjustments should be guided by clinical response (refer to the complete prescribing information for the calcium channel blocker).
HMG-CoA reductase inhibitors: Atorvastatin Pravastatin Simvastatin	↓ atorvastatin[a] ↓ pravastatin[a] ↓ simvastatin[a]	Plasma concentrations of atorvastatin, pravastatin, and simvastatin decreased. Consult the complete prescribing information for the HMG-CoA reductase inhibitor for guidance on individualizing the dose.
Hormonal contraceptives: Oral Ethinyl estradiol/ Norgestimate	↓ active metabolites of norgestimate[a]	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[a]	Coadministration in HIV-infected individuals with a history of injection drug use resulted in decreased plasma levels of methadone and signs of opiate withdrawal. Methadone dose was increased by a mean of 22% to alleviate withdrawal symptoms. Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.

[a] *See Clinical Pharmacology (12.3, Tables 8 & 9)* for magnitude of established interactions.
[b] This table is not all-inclusive.

Other Drugs

Based on the results of drug interaction studies [see *Clinical Pharmacology (12.3, Tables 8* and *9)*], no dosage adjustment is recommended when efavirenz is given with the following: aluminum/magnesium hydroxide antacids, azithromycin, cetirizine, famotidine, fluconazole, lamivudine, lorazepam, nelfinavir, paroxetine, tenofovir disoproxil fumarate, and zidovudine.

Specific drug interaction studies have not been performed with efavirenz 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 observed in non-HIV-infected volunteers receiving efavirenz when the Microgenics CEDIA DAU Multi-Level THC assay was used for screening. Negative results were obtained when more specific confirmatory testing was performed with gas chromatography/mass spectrometry.

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

ACTG 382 is an ongoing, open-label study in 57 NRTI-experienced pediatric patients to characterize the safety, pharmacokinetics, and antiviral activity of efavirenz in combination with nelfinavir (20-30 mg/kg three times daily) and NRTIs. Mean age was 8 years (range 3-16). Efavirenz has not been studied in pediatric patients below 3 years of age or who weigh less than 13 kg. At 48 weeks, the type and frequency of adverse experiences was generally similar to that of adult patients with the exception of a higher incidence of rash, which was reported in 46% (26/57) of pediatric patients compared to 26% of adults, and a higher frequency of Grade 3 or 4 rash reported in 5% (3/57) of pediatric patients compared to 0.9% of adults [see *Warnings and Precautions (5.7)* and *Adverse Reactions (6.1, Table 5; 6.2)*].

The starting dose of efavirenz was 600 mg once daily adjusted to body size, based on weight, targeting AUC levels in the range of 190-380 µM•h [see *Dosage and Administration (2.2)*]. The pharmacokinetics of efavirenz in pediatric patients were similar to the pharmacokinetics in adults who received 600-mg daily doses of efavirenz. In 48 pediatric patients receiving the equivalent of a 600-mg dose of efavirenz, steady-state C_{max} was 14.2 ± 5.8 µM (mean ± SD), steady-state C_{min} was 5.6 ± 4.1 µM, and AUC was 218 ± 104 µM•h.

8.5 Geriatric Use

Clinical studies of efavirenz 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

The pharmacokinetics of efavirenz have not been adequately studied in patients with hepatic impairment. 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 efavirenz to these patients [see *Warnings and Precautions (5.8)*].

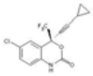
10 OVERDOSAGE

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

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

11 DESCRIPTION

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).

Efavirenz is available as film-coated tablets for oral administration containing 200 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® Brown. Opadry® Brown contains HPMC 2910/Hypromellose, titanium dioxide, macrogol/PEG 400, iron oxide yellow, iron oxide red and iron oxide black.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.3 Pharmacokinetics

Adults: The rate and extent of absorption of efavirenz from the 600 mg tablets were bioequivalent to that from SUSTIVA® tablets containing efavirenz 600 mg when administered to healthy volunteers in the fasted state.

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 efavirenz 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:

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 (17.3)*.

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 efavirenz 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

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.

Drug Interaction Studies

Efavirenz has been shown *in vivo* to cause hepatic enzyme induction, thus increasing the biotransformation of some drugs metabolized by CYP3A. *In vitro* studies have shown that efavirenz inhibited CYP isozymes 2C9, 2C19, and 3A4 with K_i values (8.5-17 μM) in the range of observed efavirenz plasma concentrations. In *in vitro* studies, efavirenz did not inhibit CYP2E1 and inhibited CYP2D6 and CYP1A2 (K_i values 82-160 μM) only at concentrations well above those achieved clinically. The inhibitory effect on CYP3A is 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 3A isozymes may result in altered plasma concentrations of the coadministered drug. Drugs which induce CYP3A activity would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations.

Drug interaction studies were performed with efavirenz and other drugs likely to be coadministered or drugs commonly used as probes for pharmacokinetic interaction. The effects of coadministration of efavirenz on the C_{max}, AUC, and C_{min} are summarized in Table 8 (effect of efavirenz on other drugs) and Table 9 (effect of other drugs on efavirenz). For information regarding clinical recommendations see *Contraindications (4.2)* and *Drug Interactions (7.1)*.

Table 8: 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 d 1-10 (pm), then 400 mg qd/ritonavir 100 mg qd d 11-24 (pm) (simultaneously with efavirenz)	600 mg qd with a light snack d 11-24 (pm)	14	↓ 17% (8-27%)	↔	↓ 42% (31-51%)
Indinavir	1000 mg q8h x 10 days After morning dose	600 mg x 10 days	20	↔[b]	↓ 33%[b] (26-39%)	↓ 39%[b] (24-51%)
	After afternoon dose			↔[b]	↓ 37%[b] (26-46%)	↓ 52%[b] (47-57%)
	After evening dose			↓ 29%[b] (11-43%)	↓ 46%[b] (37-54%)	↓ 57%[b] (50-63%)
Lopinavir/ ritonavir	400/100 mg q12h x 9 days	600 mg x 9 days	11,7[c]	↔[d]	↓ 19%[d] (↓ 36-↑ 3%)	↓ 39%[d] (3-62%)
	600/150 mg tablet q12h x 10 days with efavirenz compared to 400/100 mg q12h alone	600 mg x 9 days	23	↑ 36%[d] (28-44%)	↑ 36%[d] (28-44%)	↑ 32%[d] (21-44%)
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%)	↓ 43% (21-59%)
Ritonavir	500 mg q12h x 8 days	600 mg x 10 days	11			
	After AM dose			↑ 24% (12-38%)	↑ 18% (6-33%)	↑ 42% (9-86%)[e]
	After PM dose			↔	↔	↑ 24% (3-50%)[e]
Saquinavir SGC[f]	1200 mg q8h x 10 days	600 mg x 10 days	12	↓ 50% (28-66%)	↓ 62% (45-74%)	↓ 56% (16-77%)[e]
Lamivudine	150 mg q12h x 14 days	600 mg x 14 days	9	↔	↔	↑ 265% (37-873%)
Tenofovir[g]	300 mg qd	600 mg x 14 days	29	↔	↔	↔
Zidovudine	300 mg q12h x 14 days	600 mg x 14 days	9	↔	↔	↑ 225% (43-640%)
Azithromycin	600 mg single dose	400 mg x 7 days	14	↑ 22% (4-42%)	↔	NA
Clarithromycin	500 mg q12h x 7 days	400 mg x 7 days	11	↓ 26% (15-35%)	↓ 39% (30-46%)	↓ 53% (42-63%)
14-OH metabolite				↑ 49% (32-69%)	↑ 34% (18-53%)	↑ 26% (9-45%)
Fluconazole	200 mg x 7 days	400 mg x 7 days	10	↔	↔	↔
Itraconazole	200 mg q12h x 28 days	600 mg x 14 days	18	↓ 37% (20-51%)	↓ 39% (21-53%)	↓ 44% (27-58%)
Hydroxyitraconazole				↓ 35% (12-52%)	↓ 37% (14-55%)	↓ 43% (18-60%)
Rifabutin	300 mg qd x 14 days	600 mg x 14 days	9	↓ 32% (15-46%)	↓ 38% (28-47%)	↓ 45% (31-56%)
Voriconazole	400 mg po q12h x 1 day then 200 mg po q12h x 8 days	400 mg x 9 days	NA	↓ 61%[h]	↓ 77%[h]	NA
	300 mg po q12h days 2-7	300 mg x 7 days	NA	↓ 36%[i] (21-49%)	↓ 55%[i] (45-62%)	NA
	400 mg po q12h days 2-7	300 mg x 7 days	NA	↑ 23%[i] (↓ 1-↑ 53%)	↓ 7%[i] (↓ 23-↑ 13%)	NA
Atorvastatin	10 mg qd x 4 days	600 mg x 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 x 4 days	600 mg x 15 days	13	↓ 32% (↓59-↑ 12%)	↓ 44% (26-57%)	↓ 19% (0-35%)
Simvastatin	40 mg qd x 4 days	600 mg x 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 x 3 days, 200 mg bid x 3 days, then 400 mg qd x 29 days	600 mg x 14 days	12	↓ 20% (15-24%)	↓ 27% (20-33%)	↓ 35% (24-44%)
Epoxide metabolite				↔	↔	↓ 13% (↓30-↑ 7%)
Cetirizine	10 mg single dose	600 mg x 10 days	11	↓ 24% (18-30%)	↔	NA
Diltiazem	240 mg x 21 days	600 mg x 14 days	13	↓ 60% (50-68%)	↓ 69% (55-79%)	↓ 63% (44-75%)
Desacetyl diltiazem				↓ 64% (57-69%)	↓ 75% (59-84%)	↓ 62% (44-75%)
N-monodesmethyl diltiazem				↓ 28% (7-44%)	↓ 37% (17-52%)	↓ 37% (17-52%)
Ethinyl estradiol/ Norgestimate	0.035 mg/ 0.25 mg x 14 days	600 mg x 14 days				
Ethinyl estradiol			21	↔	↔	↔
Norelgestromin			21	↓ 46% (39-52%)	↓ 64% (62-67%)	↓ 82% (79-85%)
Levonorgestrel			6	↓ 80% (77-83%)	↓ 83% (79-87%)	↓ 86% (80-90%)
Lorazepam	2 mg single dose	600 mg x 10 days	12	↑ 16% (2-32%)	↔	NA
Methadone	Stable maintenance 35-100 mg daily	600 mg x 14-21 days	11	↓ 45% (25-59%)	↓ 52% (33-66%)	NA
Paroxetine	20 mg qd x 14 days	600 mg x 14 days	16	↔	↔	↔
Sertraline	50 mg qd x 14 days	600 mg x 14 days	13	↓ 29% (15-40%)	↓ 39% (27-50%)	↓ 46% (31-58%)

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

a Compared with atazanavir 400 mg qd alone.

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

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

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

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Efavirenz (mean % change) C_{max} (90% CI)	AUC (90% CI)	C_{min} (90% CI)
Indinavir	800 mg q8h x 14 days	200 mg x 14 days	11	↔	↔	↔
Lopinavir/ ritonavir	400/100 mg q12h x 9 days	600 mg x 9 days	11,12[a]	↔	↓ 16% (↓ 38-↑ 15%)	↓ 16% (↓ 42-↑ 20%)
Nelfinavir	750 mg q8h x 7 days	600 mg x 7 days	10	↓ 12% (↓ 32-↑ 13%)[b]	↓ 12% (↓ 35-↑ 18%)[b]	↓ 21% (↓ 53-↑ 33%)
Ritonavir	500 mg q12h x 8 days	600 mg x 10 days	9	↑ 14% (4-26%)	↑ 21% (10-34%)	↑ 25% (7-46%)[b]
Saquinavir SGC[c]	1200 mg q8h x 10 days	600 mg x 10 days	13	↓ 13% (5-20%)	↓ 12% (4-19%)	↓ 14% (2-24%)[b]
Tenofovir[d]	300 mg qd	600 mg x 14 days	30	↔	↔	↔
Azithromycin	600 mg single dose	400 mg x 7 days	14	↔	↔	↔
Clarithromycin	500 mg q12h x 7 days	400 mg x 7 days	12	↑ 11% (3-19%)	↔	↔
Fluconazole	200 mg x 7 days	400 mg x 7 days	10	↔	↑ 16% (6-26%)	↑ 22% (5-41%)
Itraconazole	200 mg q12h x 14 days	600 mg x 28 days	16	↔	↔	↔
Rifabutin	300 mg qd x 14 days	600 mg x 14 days	11	↔	↔	↓ 12% (↓ 24-↑ 1%)
Rifampin	600 mg x 7 days	600 mg x 7 days	12	↓ 20% (11-28%)	↓ 26% (15-36%)	↓ 32% (15-46%)
Voriconazole	400 mg po q12h x 1 day, then 200 mg po q12h x 8 days	400 mg x 9 days	NA	↑ 38%[e]	↑ 44%[e]	NA
	300 mg po q12h days 2-7	300 mg x 7 days	NA	↓ 14%[f] (7-21%)	↔[f]	NA
	400 mg po q12h days 2-7	300 mg x 7 days	NA	↔[f]	↑ 17%[f] (6-29%)	NA
Atorvastatin	10 mg qd x 4 days	600 mg x 15 days	14	↔	↔	↔
Pravastatin	40 mg qd x 4 days	600 mg x 15 days	11	↔	↔	↔
Simvastatin	40 mg qd x 4 days	600 mg x 15 days	14	↓ 12% (↓ 28-↑ 8%)	↔	↓ 12% (↓ 25-↑ 3%)
Aluminium hydroxide 400 mg magnesium hydroxide 400 mg, plus simethicone 40 mg	30 mL single dose	400 mg single dose	17	↔	↔	NA
Carbamazepine	200 mg qd x 3 days, 200 mg bid x 3 days, then 400 mg qd x 15 days	600 mg x 35 days	14	↓ 21% (15-26%)	↓ 36% (32-40%)	↓ 47% (41-53%)
Cetirizine	10 mg single dose	600 mg x 10 days	11	↔	↔	↔
Diltiazem	240 mg x 14 days	600 mg x 28 days	12	↑ 16% (6-26%)	↑ 11% (5-18%)	↑ 13% (1-26%)
Ethinyl estradiol	50 mcg single dose	400 mg x 10 days	13	↔	↔	↔
Famotidine	40 mg single dose	400 mg single dose	17	↔	↔	NA
Paroxetine	20 mg qd x 14 days	600 mg x 14 days	12	↔	↔	↔
Sertraline	50 mg qd x 14 days	600 mg x 14 days	13	↑ 11% (6-16%)	↔	↔

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

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

b 95% CI.

c Soft Gelatin Capsule.

d Tenofovir disoproxil fumarate.

e 90% CI not available.

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

Antiviral Activity in Cell Culture

The concentration of EFV 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. EFV 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. EFV demonstrated additive antiviral activity without cytotoxicity against HIV-1 in cell culture when combined with the NNRTIs delavirdine (DLV) and nevirapine (NVP), NRTIs (abacavir, didanosine, emtricitabine, lamivudine [LAM], stavudine, tenofovir, zalcitabine, zidovudine [ZDV]), PIs (amprenavir, indinavir [IDV], lopinavir, nelfinavir, ritonavir, saquinavir), and the fusion inhibitor enfuvirtide. EFV demonstrated additive to antagonistic antiviral activity in cell culture with atazanavir. EFV was not antagonistic with adefovir, used for the treatment of hepatitis B virus infection, or ribavirin, used in combination with interferon for the treatment of hepatitis C virus infection.

Resistance

In cell culture

In cell culture, HIV-1 isolates with reduced susceptibility to EFV (>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 RT.

Clinical studies

Clinical isolates with reduced susceptibility in cell culture to EFV have been obtained. One or more RT substitutions at amino acid positions 98, 100, 101, 103, 106, 108, 188, 190, 225, and 227 were observed in patients failing treatment with EFV in combination with IDV, or with ZDV plus LAM. The mutation K103N was the most frequently observed. Long-term resistance surveillance (average 52 weeks, range 4-106 weeks) analyzed 28 matching baseline and virologic failure isolates. Sixty-one percent (17/28) of these failure isolates had decreased EFV susceptibility in cell culture with a median 88-fold change in EFV 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 EFV-resistant were also phenotypically resistant in cell culture to DLV and NVP compared to baseline. DLV- and/or NVP-resistant clinical viral isolates with NNRTI resistance-associated substitutions (A98G, L100I, K101E/P, K103N/S, V106A, Y181X, Y188X, G190X, P225H, F227L, or M230L) showed reduced susceptibility to EFV in cell culture. Greater than 90% of NRTI-resistant clinical isolates tested in cell culture retained susceptibility to EFV.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

Study 006, a randomized, open-label trial, compared efavirenz (600 mg once daily) + zidovudine (ZDV, 300 mg q12h) + lamivudine (LAM, 150 mg q12h) or efavirenz (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/mm³ and the median baseline HIV-1 RNA level was 4.8 log10 copies/mL. Treatment outcomes with standard assay (assay limit 400 copies/mL) through 48 and 168 weeks are shown in Table 10. Plasma HIV RNA levels were quantified with standard (assay limit 400 copies/mL) and ultrasensitive (assay limit 50 copies/mL) versions of the AMPLICOR HIV-1 MONITOR assay. During the study, version 1.5 of the assay was introduced in Europe to enhance detection of non-clade B virus.

Table 10: Outcomes of Randomized Treatment Through 48 and 168 Weeks, Study 006

Outcome	Efavirenz + ZDV +LAM n=422 Week 48	Week 168	Efavirenz + IDV n=429 Week 48	Week 168	IDV + ZDV + LAM n=415 Week 48	Week 168
Responder[a]	69%	48%	57%	40%	50%	29%
Virologic failure[b]	6%	12%	15%	20%	13%	19%
Discontinued for adverse events	7%	8%	6%	8%	16%	20%
Discontinued for other reasons[c]	17%	31%	22%	32%	21%	32%
CD4+ cell count (cells/mm³)						
Observed subjects (n)	(279)	(205)	(256)	(158)	(228)	(129)
Mean change from baseline	190	329	191	319	180	329

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

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

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

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

ACTG 364 is a randomized, double-blind, placebo-controlled, 48-week study in NRTI-experienced patients who had completed two prior ACTG studies. One-hundred ninety-six patients (mean age 41 years [range 18-76], 74% Caucasian, 88% male) received NRTIs in combination with efavirenz (600 mg once daily), or nelfinavir (NFV, 750 mg three times daily), or efavirenz (600 mg once daily) + nelfinavir in a randomized, double-blinded manner. The mean baseline CD4+ cell count was 389 cells/mm³ and mean baseline HIV-1 RNA level was 8130 copies/mL. Upon entry into the study, all patients were assigned a new open-label NRTI regimen, which was dependent on their previous NRTI treatment experience. There was no significant difference in the mean CD4+ cell count among treatment groups; the overall mean increase was approximately 100 cells at 48 weeks among patients who continued on study regimens. Treatment outcomes are shown in Table 11. Plasma HIV RNA levels were quantified with the AMPLICOR HIV-1 MONITOR assay using a lower limit of quantification of 500 copies/mL.

Table 11: Outcomes of Randomized Treatment Through 48 Weeks, Study ACTG 364*

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

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

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

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

c See *Adverse Reactions (6.1)* for a safety profile of these regimens.

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Tablets

Efavirens Tablets, 200 mg are cross scored off-white colored, circular, biconvex, film coated tablets with cross score line on one side and plain on other side and are available as:

Bottles of 90 tablets; NDC- 64380 - 706 - 05

16.2 Storage

Efavirenz tablets should be stored at 20° to 25° C (68° to 77° F) [See USP Controlled Room Temperature]

16.3 Handling

If a tablet needs to be split, rest the tablet on a flat surface with the cross score lines facing up, and using fingers press down on opposite edges at the same time.

17 PATIENT COUNSELING INFORMATION

See *FDA-Approved Patient Labeling*.

17.1 Drug Interactions

A statement to patients and healthcare providers is included on the product's bottle labels: *ALERT: Find out about medicines that should NOT be taken with efavirenz.*

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

17.2 General Information for Patients

Patients should be informed that efavirenz is not a cure for HIV-1 infection and that they may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician while taking efavirenz. Patients should be told that the use of efavirenz has not been shown to reduce the risk of transmitting HIV-1 to others through sexual contact or blood contamination.

17.3 Dosing Instructions

Patients should be advised to take efavirenz every day as prescribed. Efavirenz must always be used in combination with other antiretroviral drugs. Patients should be advised to take efavirenz on an empty stomach, preferably at bedtime. Taking efavirenz with food increases efavirenz concentrations and may increase the frequency of adverse reactions. Dosing at bedtime may improve the tolerability of nervous system symptoms [see *Dosage and Administration (2)* and *Adverse Reactions (6.1)*].

17.4 Nervous System Symptoms

Patients should be informed that central nervous system symptoms (NSS) including dizziness, insomnia, impaired concentration, drowsiness, and abnormal dreams are commonly reported during the first weeks of therapy with efavirenz [see *Warnings and Precautions (5.5)*]. Dosing at bedtime may improve the tolerability of these symptoms, which are likely to improve with continued therapy. Patients should be alerted to the potential for additive effects when efavirenz is used concomitantly with alcohol or psychoactive drugs. Patients should be instructed that if they experience NSS they should avoid potentially hazardous tasks such as driving or operating machinery.

17.5 Psychiatric Symptoms

Patients should be informed that serious psychiatric symptoms including severe depression, suicide attempts, aggressive behavior, delusions, paranoia, and psychosis-like symptoms have been reported in patients receiving efavirenz [see *Warnings and Precautions (5.4)*]. If they experience severe psychiatric adverse experiences they should seek immediate medical evaluation. Patients should be advised to inform their physician of any history of mental illness or substance abuse.

17.6 Rash

Patients should be informed that a common side effect is rash [see *Warnings and Precautions (5.7)*]. Rashes usually go away without any change in treatment. However, since rash may be serious, patients should be advised to contact their physician promptly if rash occurs.

17.7 Reproductive Risk Potential

Women receiving efavirenz should be instructed to avoid pregnancy [see *Warnings and Precautions (5.6)*]. A reliable form of barrier contraception must always be used in combination with other methods of contraception, including oral or other hormonal contraception. Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of efavirenz is recommended. Women should be advised to notify their physician if they become pregnant or plan to become pregnant while taking efavirenz. If this drug is used during the first trimester of pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential harm to the fetus.

17.8 Fat Redistribution

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known [see *Warnings and Precautions (5.12)*].

FDA-Approved Patient Labeling

Patient Information

Efavirenz (eh-FAH-vih-rehnz)**] tablets**

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

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

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

What is efavirenz?

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

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

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

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

What are the possible side effects of efavirenz?

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

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

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

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

Other common side effects include tiredness, upset stomach, vomiting, and diarrhea. Some patients taking efavirenz have experienced increased levels of lipids (cholesterol and triglycerides) in the blood.

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

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

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

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

How should I take efavirenz?

General Information

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

Tablets

- The dose of efavirenz tablets for adults is 600 mg once a day by mouth. The dose of efavirenz for children may be lower (see **Can children take efavirenz?**).

Can children take efavirenz?

Yes, children who are able to swallow tablets can take efavirenz. Rash may be a serious problem in some children. Tell your child's doctor right away if you notice rash or any other side effects while your child is taking efavirenz. The dose of efavirenz for children may be lower than the dose for adults. Tablets containing lower doses of efavirenz are available. Your child's doctor will determine the right dose based on your child's weight.

If a tablet needs to be split, rest the tablet on a flat surface with the cross score lines facing up, and using fingers press down on opposite edges at the same time.

Who should not take efavirenz?

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

What should I avoid while taking efavirenz?

- **Women should not become pregnant while taking efavirenz and for 12 weeks after stopping it.** Serious birth defects have been seen in the offspring of animals and women treated with efavirenz during pregnancy. It is not known whether efavirenz caused these defects. **Tell your doctor right away if you are pregnant.** Also talk with your doctor if you want to become pregnant.
- Women should not rely only on hormone-based birth control, such as pills, injections, or implants, because efavirenz may make these contraceptives ineffective. Women must use a reliable form of barrier contraception, such as a condom or diaphragm, even if they also use other methods of birth control. Efavirenz may remain in your blood for a time after therapy is stopped. Therefore, you should continue to use contraceptive measures for 12 weeks after you stop taking efavirenz.
- **Do not breast-feed if you are taking efavirenz.** The Centers for Disease Control and Prevention recommend that mothers with HIV not breast-feed because they can pass the HIV through their milk to the baby. Also, efavirenz may pass through breast milk and cause serious harm to the baby. Talk with your doctor if you are breast-feeding. You may need to stop breast-feeding or use a different medicine.
- Taking efavirenz with alcohol or other medicines causing similar side effects as efavirenz, such as drowsiness, may increase those side effects.
- Do not take any other medicines without checking with your doctor. These medicines include prescription and nonprescription medicines and herbal products, especially St. John's wort *(Hypericum perforatum)*.

Before using efavirenz, tell your doctor if you

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

What important information should I know about taking other medicines with efavirenz?

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

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

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

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

MEDICINES YOU SHOULD NOT TAKE WITH EFAVIRENZ

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

- Vascor (bepridil)
- Propulsid (cisapride)
- Versed (midazolam)
- Orap (pimozide)
- Halcion (triazolam)
- Ergot medications (for example, Wigraine and Cafergot)

The following medicines should not be taken with efavirenz since they contain the active ingredient efavirenz:

- ATRIPLA (efavirenz, emtricitabine, tenofovir disoproxil fumarate)
- SUSTIVA (efavirenz)

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

- Fortovase, Invirase (saquinavir)
- Biaxin (clarithromycin)
- Carbatrol, Tegretol (carbamazepine)
- Sporanox (itraconazole)
- REYATAZ (atazanavir sulfate), if this is not the first time you are receiving treatment for your HIV infection

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

- Calcium channel blockers such as Cardizem or Tiazac (diltiazem), Covera HS or Isoptin SR (verapamil), and others.
- The cholesterol-lowering medicines Lipitor (atorvastatin), PRAVACHOL (pravastatin sodium), and Zocor (simvastatin).
- Crixivan (indinavir)
- Kaletra (lopinavir/ritonavir)
- Methadone
- Mycobutin (rifabutin)
- REYATAZ (atazanavir sulfate). If you are taking efavirenz and REYATAZ, you should also be taking Norvir (ritonavir).
- Rifadin (rifampin) or the rifampin-containing medicines Rifamate and Rifater.
- Vfend (voriconazole) and efavirenz must not be taken together at standard doses. Some doses of voriconazole can be taken at the same time as a lower dose of efavirenz, but you must check with your doctor first.
- Zoloft (sertraline)
- The immunosuppressant medicines cyclosporine (Gengraf, Neoral, Sandimmune, and others), Prograf (tacrolimus), or Rapamune (sirolimus).

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

General advice about efavirenz:

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

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

Keep efavirenz out of the reach of children.

This leaflet summarizes the most important information about efavirenz. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for the full prescribing information about efavirenz.

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