



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 tablets.

Evarex Tablets

Initial U.S. Approval: 1998

Warnings and Precautions, Reproductive Risk Potential (5.6)
Warnings and Precautions, Hepatotoxicity (5.8)

RECENT MAJOR CHANGES

3/2010
3/2010

INDICATIONS AND USAGE

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

DOSEAGE AND ADMINISTRATION

- Evarex tablets 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 capsule formulation. (2.1)

Table with 6 columns: Pediatric Patients at Least 3 Years and at Least 10 kg (2.2), kg, lbs, dose, kg, lbs, dose. Rows show dosing for 10-15, 15-20, and 20-25 kg.

DOSEAGE FORMS AND STRENGTHS

- Tablets: 600 mg. (3)

CONTRAINDICATIONS

- Evarex tablets are contraindicated in patients with previously demonstrated hypersensitivity (e.g., 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 (e.g., 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)

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- Not recommended with ATRIPLA, which contains efavirenz, emtricitabine, and tenofovir disoproxil fumarate. (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 to 2 days after initiating therapy and resolve in 2 to 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. (5.6, 17.7)
Hepatotoxicity: Monitor liver function tests before and during treatment in patients with underlying hepatic disease, including hepatitis B or C coinfection, marked transaminase elevations, or who are taking medications associated with liver toxicity. Among reported cases of hepatic failure, a few occurred in patients with no pre-existing hepatic disease. (5.8, 6.1, 8.2)
Rash: Rash usually begins within 1 to 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 Aurobindo Pharma USA, Inc. at 1-866-950-2876 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)
Hepatic impairment: Efavirenz is not recommended for patients with moderate or severe hepatic impairment. Use caution in patients with mild hepatic impairment. (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

Issued: May 2011

Table with 2 columns: Adverse Reactions, Study 006, Study ACTG 364. Rows include Indications and Usage, Overdosage, Description, Clinical Pharmacology, Clinical Studies, Nonclinical Toxicology, How Supplied/Storage and Handling, Patient Counseling Information, Drug Interaction, Laboratory Abnormalities.

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Evarex tablets in combination with other antiretroviral agents are 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 (14.1)).

2 DOSAGE AND ADMINISTRATION

2.1 Adults

The recommended dosage of efavirenz tablets 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 tablets be taken on an empty stomach, preferably at bedtime. The increased efavirenz concentrations observed following administration of efavirenz tablets 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

Evarex tablets may 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 tablets are 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 using the capsule formulation (one 200 mg and two 50 mg capsules or six 50 mg capsules). Evarex tablets should not be broken. (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 tablets be taken on an empty stomach, preferably at bedtime. Table 1 describes the recommended oral dosage of efavirenz tablets for pediatric patients 3 years of age or older and weighing between 10 and 40 kg. (See Use in Specific Populations (8.4)). The recommended dosage of efavirenz tablets for pediatric patients weighing greater than 40 kg is 600 mg once daily.

Table 1: Pediatric Dose to be Administered Once Daily

Table with 3 columns: Body Weight, lbs, Evarex Dose (mg). Rows show dosing for 10 to less than 15, 15 to less than 20, 20 to less than 25, 25 to less than 32.5, 32.5 to less than 40, and at least 40 lbs.

3 DOSAGE FORMS AND STRENGTHS

Evarex tablets 600 mg are yellow colored oval biconvex film-coated tablets debossed 'D' on one side and '37' on other side.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Evarex tablets are contraindicated in patients with previously demonstrated clinically significant hypersensitivity (e.g., 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 (e.g., cardiac arrhythmias, prolonged sedation, or respiratory depression). Drugs that are contraindicated with efavirenz tablets are listed in Table 2.

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

Table with 2 columns: Drug Class: Drug Name, Clinical Comment. Lists contraindications for Antimigraine, Benzodiazepines, Calcium channel blocker, GI motility agent, Neuroleptic, and St. John's wort.

5 WARNINGS AND PRECAUTIONS

5.1 Drug Interactions

Evarex 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

Evarex 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 account the potential for viral cross-resistance. (See Warnings and Precautions (5.4)).

5.3 Concomitant Use with Related Products

Coadministration of efavirenz with ATRIPLA (efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) is not recommended, since efavirenz is one of its 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 (±1) years and 635 patients treated with control regimens for a mean (±1) 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%, 0.5%), suicidal ideation (0.7%, 0.3%), nonfatal suicide attempts (0.5%, 0), aggressive behavior (0.4%, 0.2%), paranoid reactions (0.4%, 0.3%), and manic reactions (0.3%, 0.2%). 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 selected psychiatric symptoms included history of injecting 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 interrupted treatment because of one or more of the following nervous system symptoms: dizziness, insomnia, 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.

5.5 Nervous System Symptoms

Fifty-three percent (53/1008) 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 (23.1% of the 1008 patients), insomnia (16.3%), impaired concentration (6.3%), somnolence (7%), abnormal dreams (6.2%), and hallucinations (1.2%). These symptoms were severe in 2% of patients, and 2.1% of patients discontinued therapy as a result. These symptoms usually began during the first or second day of therapy and generally resolved after the first 2 to 4 weeks of therapy. After a single case of anophthalmia with first-trimester exposure to efavirenz has also been reported; however, this case included severe oblique facial clefts and anophthalmic band, 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 the less frequent psychiatric symptoms. (See Warnings and Precautions (5.4)). Liver enzyme monitoring with efavirenz has also been reported; however, this case included severe oblique facial clefts and anophthalmic band, 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 the less frequent psychiatric symptoms. (See Warnings and Precautions (5.4)). Liver enzyme monitoring with efavirenz has also been reported; however, this case included severe oblique facial clefts and anophthalmic band, a known association with anophthalmia. There have been six retrospective reports of findings consistent with neural tube defects, including meningomyelocele. 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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 Interference

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 THU assay was used for screening. Negative results were obtained when more specific chromatography testing was performed with gas chromatography/mass spectrometry.

Of the three assays analyzed (Microgenics CEDIA DAU Multi-Level THU assay, Cannabinoid Enzyme Immunoassay [Diagnostic Reagents, Inc.] and AxSYM Cannabinoid Assay), only the Microgenics CEDIA DAU Multi-Level THU 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 nevirapin (20 to 30 mg/kg three times daily) and NRTIs. Mean age was 8 years (range 3 to 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 mean AUC of efavirenz was 600 mg once daily adjusted to body size, based on weight, targeting AUC levels in the range of 190 to 300 µM<sup>h</sup> *[see Dosage and Administration (2.2)].* The pharmacokinetics of efavirenz in pediatric patients compared 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 ± 6.6 µM (mean ± SD), steady-state  $C_{min}$  was 5.6 ± 4.1 µM, and AUC was 216 ± 104 µM<sup>h</sup>.

### 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

Efavirenz 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 efavirenz to these patients. *[see Warnings and Precautions (5.8) and Clinical Pharmacology (12.3)].*

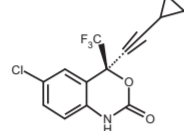
## 10 OVERDOSAGE

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

Treatment of overdose with efavirenz should consist of general supportive measures, including monitoring of vital signs and observation of the patient's clinical response. Administered doses 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 (NRTI). Efavirenz is chemically described as (S)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one. Its molecular formula is C<sub>16</sub>H<sub>12</sub>ClF<sub>3</sub>N<sub>2</sub>O<sub>2</sub> 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 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 hydroxypropyl cellulose, polyethylene glycol, titanium dioxide, and yellow iron oxide.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

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

### 12.3 Pharmacokinetics

Peak efavirenz plasma concentrations of 1.6 to 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 to 5 hours and steady-state plasma concentrations were reached in 6 to 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<sup>h</sup>.

### Effect of Food on Oral Absorption

Administration of a single 600 mg efavirenz tablet with a high-fat/high-caloric meal (approximately 1000 kcal, 500 to 600 kcal from fat) was associated with a 28% increase in mean AUC<sub>0-∞</sub> 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)].*

Efavirenz is highly bound (approximately 99.5 to 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 to 400 mg per day for 10 days resulted in a lower than predicted extent of accumulation (22 to 42% lower) and a shorter terminal half-life of 40 to 55 hours (single dose half-life 32 to 76 hours).

### Elimination

Efavirenz has a terminal half-life of 52 to 76 hours after single doses and 40 to 55 hours after multiple doses. A one-month mass balance/excretion study was conducted using 400 mg per day with a <sup>14</sup>C-labeled dose administered on Day 8. Approximately 14 to 34% of the radiolabel was recovered in the urine and 16 to 61% was recovered in the feces, likely 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.

**Hepatic impairment:** A multiple-dose study showed no significant effect on efavirenz pharmacokinetics in patients with mild hepatic impairment (Child-Pugh Class A). A controlled study with 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. *In vitro* studies have shown that efavirenz inhibited CYP isozymes 2C9, 2C19, and 3A4 with  $K_i$  values (6.5 to 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 to 160 µM) only at concentrations well above those achieved clinically. The inhibitory effect of 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 CYP3A 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 results likely to be coadministered or drugs commonly used as probes for pharmacokinetic interactions. 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 1 to 20 400 mg qd d 1 to 6, then 300 mg qd with ritonavir 100 mg qd and a light meal	600 mg qd with a light meal 7 to 20	27	↓ 59% <sup>a</sup> (40-67%)	↓ 74% <sup>a</sup> (62-87%)	↓ 95% <sup>a</sup> (82-100%)
		600 mg qd	13	↓ 114% <sup>b</sup> (↓ 17-1 58%)	↓ 139% <sup>b</sup> (↓ 2-88%)	↓ 48% <sup>b</sup> (↓ 24-76%)
		600 mg qd with ritonavir 100 mg qd and a light meal	14	↑ 17% <sup>a</sup> (8-27%)	↔	↓ 42% <sup>a</sup> (31-51%)
		300 mg qd/ritonavir 100 mg qd d 1 to 10 (pm), then 400 mg qd/ritonavir 100 mg qd d 11 to 24 (pm) (simultaneous with efavirenz)	14	↑ 17% <sup>a</sup> (8-27%)	↔	↓ 42% <sup>a</sup> (31-51%)
Indinavir	1000 mg q 8 h x 10 days	600 mg qd x 10 days	20	↔ <sup>b</sup>	↔ <sup>b</sup>	↔ <sup>b</sup>
		After morning dose	↔ <sup>b</sup>	↓ 33% <sup>b</sup> (26-39%)	↓ 39% <sup>b</sup> (24-51%)	
	After afternoon dose	↔ <sup>b</sup>	↔ <sup>b</sup>	↓ 52% <sup>b</sup> (26-64%)		
	After evening dose	↔ <sup>b</sup>	↓ 29% <sup>b</sup> (11-43%)	↓ 46% <sup>b</sup> (31-62%)		
Lopinavir/ritonavir	400/100 mg capsule q 12 h x 9 days	600 mg qd x 9 days	11, <sup>2*</sup>	↔ <sup>a</sup>	↓ 19% <sup>a</sup> (↓ 36-1 3%)	↓ 39% <sup>a</sup> (3-62%)
		600/150 mg tablet q 12 h x 10 days with efavirenz 600 mg qd x 14 days	23	↑ 36% <sup>d</sup> (28-44%)	↑ 36% <sup>d</sup> (28-44%)	↑ 32% <sup>d</sup> (21-44%)
Nefirnavir	750 mg q 8 h x 7 days	600 mg qd x 7 days	10	↑ 21% (10-33%)	↑ 20% (8-34%)	↔
		Metabolite AG-1402	↔	↓ 40% (30-48%)	↓ 37% (25-48%)	↓ 43% (21-59%)
		After AM dose	↔	124% (12-38%)	118% (6-33%)	142% (9-86%)
	After PM dose	↔	↔	↔	↑ 24% (3-50%) <sup>d</sup>	
Saqiunavir SDC <sup>†</sup>	1200 mg q 8 h x 10 days	600 mg qd x 10 days	12	↓ 50% (28-66%)	↓ 62% (45-74%)	↓ 56% (20-82%) <sup>d</sup>
		Lamivudine	150 mg q 12 h x 14 days	9	↔	↔
Tenofovir <sup>‡</sup>	300 mg qd	600 mg qd x 14 days	29	↔	↔	↔
Zidovudine	300 mg q 12 h x 14 days	600 mg qd x 14 days	9	↔	↔	↑ 225% (43-640%)
Maraviroc	100 mg bid	600 mg qd	12	↓ 51% (37-62%)	↓ 45% (38-51%)	↓ 45% (28-57%)
		Azithromycin	600 mg qd	14	↑ 22% (14-28%)	↔
Clarithromycin	500 mg q 12 h x 7 days	400 mg qd 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 qd x 7 days	10	↔	↔	↔
		Itraconazole	200 mg q 12 h x 28 days	18	↓ 37% (20-51%)	↓ 39% (21-53%)
Hydroxyitraconazole	200 mg q 12 h x 28 days	400 mg qd x 14 days	18	↓ 35% (12-52%)	↓ 37% (14-55%)	↓ 43% (18-60%)
		Posaconazole	400 mg (oral suspension) bid x 10 and 20 days	11	↓ 45% (34-53%)	NA
Rifabutin	300 mg qd x 14 days	600 mg qd x 14 days	9	↓ 32% (15-46%)	↓ 38% (22-47%)	↓ 45% (31-59%)
		Voriconazole	400 mg po q 12 h x 1 day then 200 mg po q 12 h x 8 days	NA	↑ 61% <sup>b</sup> (41-83%)	↑ 77% <sup>b</sup> (57-97%)
Voronazole	400 mg po q 12 h x 1 day then 200 mg po q 12 h x 8 days	600 mg qd x 9 days	NA	↑ 36% <sup>d</sup> (21-49%)	↑ 36% <sup>d</sup> (45-62%)	NA
		300 mg po q 12 h days 2 to 7	NA	↑ 23% <sup>d</sup> (↓ 1-53%)	↑ 7% <sup>d</sup> (↓ 23-1 3%)	NA
Atorvastatin	10 mg qd x 4 days	600 mg qd x 15 days	14	↓ 14% (↓ 28%)	↓ 43% (↓ 26%)	↓ 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 qd x 15 days	13	↓ 32% (↓ 59-1 2%)	↓ 44% (26-57%)	↓ 19% (0-35%)
		Simvastatin	40 mg qd x 4 days	14	↓ 72% (2-32%)	↓ 68% (62-73%)
Carbamazepine	200 mg qd x 3 days, then 400 mg qd x 29 days	600 mg qd x 14 days	12	↓ 20% (15-24%)	↓ 27% (20-33%)	↓ 35% (24-44%)
		Epoxide metabolite	↔	↔	↔	↓ 13% (↓ 30-1 7%)
Diltiazem	10 mg single dose	600 mg qd x 10 days	11	↑ 24% (18-30%)	↔	NA
		Diltiazem	240 mg x 21 days	13	↓ 60% (50-68%)	↓ 69% (55-79%)
Desacetil diltiazem	10 mg single dose	600 mg qd x 10 days	12	↓ 64% (57-69%)	↓ 75% (59-84%)	↓ 62% (44-75%)
		N-monomethyl efavirenz	↔	↓ 28% (7-44%)	↓ 37% (17-52%)	↓ 37% (17-52%)
Ethinyl estradiol/Norgestimate	0.035 mg/0.25 mg x 14 days	600 mg qd x 14 days	21	↔	↔	↔
		Ethinyl estradiol	21	↔	↔	↔
Norelgestromin/Norgestrel	2 mg single dose	600 mg qd x 10 days	12	↓ 16% (2-32%)	↔	NA
		Lorazepam	2 mg single dose	600 mg qd x 10 days	12	↓ 16% (2-32%)
Methadone	Stable maintenance 35 to 100 mg daily	600 mg qd x 14 to 21 days	11	↓ 45% (25-59%)	↓ 52% (33-66%)	NA
		Paroxetine	20 mg qd x 14 days	16	↔	↔
Sertraline	50 mg qd x 14 days	600 mg qd x 14 days	13	↓ 29% (15-40%)	↓ 39% (27-50%)	↓ 46% (31-58%)

<sup>1</sup> Indicates increase    ↓ Indicates decrease    ↔ Indicates no change or a mean increase or decrease of <10%.

<sup>2</sup> Compared with atazanavir 400 mg qd alone.

<sup>3</sup> Comparator dose of indinavir was 800 mg q 8 h x 10 days.

<sup>4</sup> Parallel-group design; n for efavirenz + lopinavir/ritonavir, n for lopinavir/ritonavir alone.

<sup>5</sup> Values are for lopinavir; the pharmacokinetics of ritonavir in this study were unaffected by concurrent efavirenz.

<sup>6</sup> 95% CI

<sup>7</sup> Soft Gelatin Capsule.

<sup>8</sup> Tenofovir disoproxil fumarate.

<sup>9</sup> 90% CI not available.

<sup>10</sup> Relative to steady-state administration of voriconazole (400 mg for 1 day, then 200 mg po q 12 h for 2 days).

<sup>11</sup> 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 q 8 h x 14 days	200 mg qd x 14 days	11	↔	↔	↔
		Lopinavir/ritonavir	400/100 mg q 12 h x 9 days	11, 12 <sup>2</sup>	↔	↓ 16% (↓ 38-1 15%)
Nefirnavir	750 mg q 8 h x 7 days	600 mg qd x 7 days	10	↓ 12% (↓ 32-1 13%) <sup>b</sup>	↓ 12% (↓ 35-1 18%) <sup>b</sup>	↓ 21% (↓ 53-1 33%)
		Ritonavir	500 mg q 12 h x 8 days	9	↑ 14% (4-26%)	↑ 21% (10-34%)
Saqiunavir SDC <sup>†</sup>	1200 mg q 8 h x 10 days	600 mg qd x 10 days	13	↓ 13% (5-20%)	↓ 12% (4-19%)	↓ 14% (2-24%) <sup>d</sup>
		Tenofovir <sup>‡</sup>	300 mg qd	30	↔	↔
Azithromycin	600 mg single dose	400 mg qd x 7 days	14	↔	↔	↔
		Clarithromycin	500 mg q 12 h x 7 days	12	↑ 11% (3-19%)	↔
Fluconazole	200 mg x 7 days	400 mg qd x 7 days	10	↔	↑ 16% (6-26%)	↑ 22% (5-41%)
		Itraconazole	200 mg q 12 h x 14 days	16	↔	↔
Rifabutin	300 mg qd x 14 days	600 mg qd x 14 days	11	↔	↔	↓ 12% (↓ 24-1 1%)
		Rifampin	600 mg qd x 7 days	12	↓ 20% (11-28%)	↓ 26% (15-36%)
Voriconazole	400 mg po q 12 h x 1 day then 200 mg po q 12 h x 8 days	600 mg qd x 9 days	NA	↑ 38% <sup>a</sup>	↑ 44% <sup>a</sup>	NA
		300 mg po q 12 h days 2 to 7	NA	↑ 14% <sup>d</sup> (7-21%)	↔	NA
Atorvastatin	10 mg qd x 4 days	600 mg qd x 15 days	14	↔	↔	↔
		Pravastatin	40 mg qd x 4 days	11	↔	↔
Simvastatin	40 mg qd x 4 days	600 mg qd x 15 days	14	↓ 12% (↓ 28-1 8%)	↔	↓ 12% (↓ 25-1 3%)
		Aluminum hydroxide 400 mg, magnesium hydroxide 400 mg, paracetamol 400 mg	30 mL single dose	17	↔	↔
Carbamazepine	200 mg qd x 3 days, 200 mg bid x 3 days, then 400 mg qd x 15 days	600 mg qd x 35 days	14	↓ 21% (15-26%)	↓ 36% (32-40%)	↓ 47% (41-53%)
		Cetirizine	10 mg single dose	600 mg qd x 10 days	11	↔
Diltiazem	240 mg x 14 days	600 mg qd x 28 days	12	↑ 16% (6-26%)	↑ 11% (5-18%)	↑ 13% (1-26%)
		Famotidine	40 mg single dose	17	↔	↔
Paroxetine	20 mg qd x 14 days	600 mg qd x 14 days	12	↔	↔	↔
		Sertraline	50 mg qd x 14 days	13	↑ 11% (6-16%)	↔

<sup>1</sup> Indicates increase    ↓ Indicates decrease    ↔ Indicates no change or a mean increase or decrease of <10%.

<sup>2</sup> Parallel-group design; n for efavirenz + lopinavir/ritonavir, n for efavirenz alone.

<sup>3</sup> 95% CI

<sup>4</sup> Soft Gelatin Capsule.

<sup>5</sup> Tenofovir disoproxil fumarate.

<sup>6</sup> 90% CI not available.

<sup>7</sup> 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 NRTI of HIV-1. EFV activity is mediated predominantly by noncompetitive inhibition of HIV-1 reverse transcriptase (RT). HIV-2 RT and human mitochondrial DNA polymerases  $\alpha$ ,  $\beta$ , <

# Patient Information

## Efavirenz Tablets

### [efavirenz (eh-FAH-vih-rehnz)]

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

Please also read the section “**MEDICINES YOU SHOULD NOT TAKE WITH EFAVIRENZ TABLETS.**”

Read this information before you start taking efavirenz tablets. Read it again each time you refill your prescription, in case there is any new information. This leaflet provides a summary about efavirenz tablets 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 are efavirenz tablets?

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

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

Efavirenz tablets have 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 tablets?

**Serious psychiatric problems.** A small number of patients experience severe depression, strange thoughts, or angry behavior while taking efavirenz tablets. 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 tablets.

**Common side effects.** Many patients have dizziness, trouble sleeping, drowsiness, trouble concentrating, and/or unusual dreams during treatment with efavirenz tablets. These side effects may be reduced if you take efavirenz tablets 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 tablets are 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 tablets.

Other common side effects include tiredness, upset stomach, vomiting, and diarrhea. Some patients taking efavirenz tablets 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.

**Liver problems.** Some patients taking efavirenz tablets have experienced serious liver problems including liver failure resulting in transplantation or death. Most of these serious side effects occurred in patients with a chronic liver disease such as hepatitis infection, but there have also been a few reports in patients without any existing liver disease.

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

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

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

#### How should I take efavirenz tablets?

##### General Information

- You should take efavirenz tablets on an empty stomach, preferably at bedtime.
- Swallow efavirenz tablets with water.
- Taking efavirenz tablets with food increases the amount of medicine in your body, which may increase the frequency of side effects.
- Taking efavirenz tablets at bedtime may make some side effects less bothersome.
- Efavirenz tablets must be taken in combination with other anti-HIV medicines. If you take only efavirenz tablets, the medicine may stop working.
- Do not miss a dose of efavirenz tablets. If you forget to take efavirenz tablets, 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 tablets 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 tablets, 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 tablets 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 (one tablet) once a day by mouth.

#### Can children take efavirenz tablets?

Yes, children who are able to swallow capsules can take efavirenz tablets. 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 tablets. The dose of efavirenz tablets for children may be lower than the dose for adults. Capsules containing lower doses of efavirenz are available. Your child’s doctor will determine the right dose based on your child’s weight.

#### Who should not take efavirenz tablets?

**Do not take efavirenz tablets 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 tablets?

- **Women should not become pregnant while taking efavirenz tablets and for 12 weeks after stopping them.** Serious birth defects have been seen in the offspring of animals and women treated with efavirenz tablets during pregnancy. It is not known whether efavirenz tablets 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 tablets 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 tablets.
- **Do not breast-feed if you are taking efavirenz tablets.** 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 tablets with alcohol or other medicines causing similar side effects as efavirenz tablets, 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 tablets, 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 tablets or may switch you to another medicine.
- **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 tablets?**

**Efavirenz tablets 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 tablets. For this reason, **it is very important to:**

- let all your doctors and pharmacists know that you take efavirenz tablets.
- 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 tablets 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 TABLETS**

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

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

The following medicine should not be taken with efavirenz tablets since they contain efavirenz, the active ingredient in efavirenz tablets:

- ATRIPLA (efavirenz, emtricitabine, tenofovir disoproxil fumarate)

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

- Fortovase, Invirase (saquinavir)
- Biaxin (clarithromycin)
- Carbatrol, Tegretol (carbamazepine)
- Noxafil (posaconazole)
- 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 tablets 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 tablets and REYATAZ, you should also be taking Norvir (ritonavir).
- Rifadin (rifampin) or the rifampin-containing medicines Rifamate and Rifater.
- Selzentry (maraviroc)
- 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.
- Zolofit (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 tablets. Be sure to tell your doctor about all medicines that you take.**

**General advice about efavirenz tablets:**

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

Keep efavirenz tablets at room temperature 20° to 25°C (68° to 77°F) in the bottle given to you by your pharmacist. The temperature can range from 15° to 30°C (59° to 86°F).

Keep efavirenz tablets out of the reach of children.

This leaflet summarizes the most important information about efavirenz tablets. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for the full prescribing information about efavirenz tablets or you can call 1-866-850-2876.

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Issued: May 2011