

Efavirenz 200 mg Capsules/Efavirenz 600 mg Tablets  
**EFAVIR**

## **COMPOSITION**

### **EFAVIR-200 Capsules**

Each hard gelatin capsule contains:  
Efavirenz ..... 200 mg

### **EFAVIR-600 Tablets**

Each film-coated tablet contains:  
Efavirenz ..... 600 mg

## **DOSAGE FORM**

Oral, hard gelatin capsule  
Oral, film-coated tablet

## **PHARMACOLOGY**

### **Pharmacodynamics**

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  $\alpha$ ,  $\beta$ ,  $\gamma$  and  $\delta$  are not inhibited by EFV.

### **Pharmacokinetics**

**Absorption:** Peak efavirenz plasma concentrations of 1.6–9.1  $\mu\text{M}$  were attained by 5 hours following single oral doses of 100 mg to 1600 mg administered to uninfected volunteers. Dose-related increases in  $C_{\text{max}}$  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  $C_{\text{max}}$ , mean  $C_{\text{min}}$ , 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  $C_{\text{max}}$  was  $12.9 \pm 3.7 \mu\text{M}$  (mean  $\pm$  SD), steady-state  $C_{\text{min}}$  was  $5.6 \pm 3.2 \mu\text{M}$ , and the AUC was  $184 \pm 73 \mu\text{M}\cdot\text{h}$

### *Effect of Food on Oral Absorption*

**Capsules:** Administration of a single 600 mg dose of efavirenz capsules with a high-fat/high-caloric meal (894 kcal, 54 g fat, 54% calories from fat) or a reduced-fat/normal-caloric meal (440 kcal, 2 g fat, 4% calories from fat) was associated with a mean increase of 22% and 17% in efavirenz  $\text{AUC}_{\infty}$  and a mean increase of 39% and 51% in efavirenz  $C_{\text{max}}$ , respectively, relative to the exposures achieved when given under fasted conditions. (see **DOSAGE AND ADMINISTRATION**)

**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  $\text{AUC}_{\infty}$  of efavirenz and a 79% increase in mean

$C_{\max}$  of efavirenz relative to the exposures achieved under fasted conditions (see **DOSAGE AND ADMINISTRATION**).

***Distribution:*** Efavirenz is highly bound (approximately 99.5–99.75%) to human plasma proteins, predominantly albumin. In HIV-1 infected patients (n=9) who received efavirenz 200 to 600 mg once daily for at least 1 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 CYP450 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 <sup>14</sup>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 the feces.

### ***Special Populations***

***Hepatic Impairment:*** The pharmacokinetics of efavirenz has not been adequately studied in patients with hepatic impairment (see **WARNINGS AND PRECAUTIONS**).

***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 has 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.

## **INDICATIONS**

**EFAVIR** (efavirenz) **Capsules and 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 a year's duration, which demonstrated prolonged suppression of HIV RNA.

## DOSAGE AND ADMINISTRATION

### Adults

The recommended dosage of **EFAVIR Capsules and Tablets** is 600 mg orally, once daily, in combination with a protease inhibitor and/or nucleoside reverse transcriptase inhibitors (NRTIs).

It is recommended that **EFAVIR Capsules and Tablets** be taken on an empty stomach, preferably at bedtime. The increased efavirenz concentrations observed following administration of **EFAVIR Capsules and Tablets** with food may lead to an increase in the frequency of adverse reactions (see **PHARMACOLOGY**). Dosing at bedtime may improve the tolerability of nervous system symptoms (see **WARNINGS AND PRECAUTIONS AND UNDESIRABLE EFFECTS**).

### Concomitant Antiretroviral Therapy

**EFAVIR Capsules and Tablets** must be given in combination with other antiretroviral medications (see **WARNINGS AND PRECAUTIONS, Drug Interactions AND PHARMACOLOGY**).

### Dosage Adjustment

If **EFAVIR Capsules and Tablets** are co-administered 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 efavirenz Capsule formulation (one 200-mg and two 50-mg capsules or six 50-mg capsules). Efavirenz tablet should not be broken.

### Pediatric

### Patients

It is recommended that **EFAVIR Capsules and Tablets** 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 and weighing between 10 and 40 kg. 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		Efavirenz Dose (mg)
kg	lbs	
10 to less than 15	22 to less than 33	200
15 to less than 20	33 to less than 44	250
20 to less than 25	44 to less than 55	300
25 to less than 32.5	55 to less than 71.5	350
32.5 to less than 40	71.5 to less than 88	400

at least 40

at least 88

600

## CONTRAINDICATIONS

### Hypersensitivity

**EFAVIR Capsules and Tablets** are 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.

### 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, methylethergonovine)	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 ( <i>Hypericum perforatum</i> )	May lead to loss of virologic response and possible resistance to efavirenz or to the class of non-nucleoside reverse transcriptase inhibitors (NNRTI).

## WARNINGS AND PRECAUTIONS

### 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** and **DRUG INTERACTIONS**).

Efavirenz has been shown *in vivo* to induce CYP3A4. Other compounds that are substrates of CYP3A4 may have decreased plasma concentrations when co-administered with efavirenz. *In vitro* studies have demonstrated that efavirenz inhibits CYP2C9, 2C19, and 3A4 isozymes in the range of observed efavirenz plasma concentrations. Co-administration of efavirenz with drugs primarily metabolized by these isozymes may result in altered plasma concentrations of

the co-administered drug. Therefore, appropriate dose adjustments may be necessary for these drugs.

Drugs that induce CYP3A4 activity (eg, 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 3, 4 and 5.

**Table 3: Established <sup>a</sup> and Other Potentially Significant <sup>b</sup> Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction**

Concomitant Drug Class: Drug Name	Effect on Concentration of Efavirenz or Concomitant Drug	Clinical Comment
<b>Antiretroviral Agents</b>		
Protease inhibitor: Fosamprenavir calcium	↓ Amprenavir	<p><i>Fosamprenavir (unboosted):</i> Appropriate doses of the combinations with respect to safety and efficacy have not been established.</p> <p><i>Fosamprenavir/ritonavir:</i> 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.</p>
Protease inhibitor: Atazanavir	↓ Atazanavir <sup>a</sup>	<p><i>Treatment naïve patients:</i> When co-administered 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</p>

		<p>an empty stomach, preferably at bedtime).</p> <p><i>Treatment-experienced patients:</i> Coadministration of efavirenz and atazanavir is not recommended.</p>
Protease inhibitor: Indinavir	↓ Indinavir <sup>a</sup>	<p>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<sub>min</sub> were decreased on average by 33–46% and 39–57% respectively, compared to when indinavir (800 mg every 8 hours) was given alone.</p>
Protease inhibitor: Lopinavir/ritonavir	↓ Lopinavir <sup>a</sup>	<p>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 600/150mg (3 tablets) twice daily may</p>

		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 oral solution to 533/133 mg (6.5 mL) twice daily taken with food is recommended when used in combination with efavirenz.
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Protease inhibitor: Ritonavir	↑ Ritonavir <sup>a</sup> ↑ Efavirenz <sup>a</sup>	When ritonavir 500 mg q12h was co-administered with efavirenz 600 mg once daily, the combination was associated with a higher frequency of adverse clinical experiences (eg, dizziness, nausea, paresthesia) and laboratory abnormalities (elevated liver enzymes). Monitoring of liver enzymes is recommended when efavirenz is used in combination with ritonavir.
Protease inhibitor: Saquinavir	↓ Saquinavir <sup>a</sup>	Should not be used as sole protease inhibitor in combination with efavirenz.
<b>Other Agents</b>		
Anticoagulant: Warfarin	↑ or ↓ Warfarin	Plasma concentrations and effects potentially increased or decreased by efavirenz.

<p>Anticonvulsants: Carbamazepine</p> <p>Phenytoin Phenobarbital</p>	<p>↓ Carbamazepine<sup>a</sup> ↓ Efavirenz<sup>a</sup></p> <p>↓ Anticonvulsant ↓ Efavirenz</p>	<p>There are insufficient data to make a dose recommendation for efavirenz. Alternative anticonvulsant treatment should be used.</p> <p>Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.</p>
<p>Antidepressant: Sertraline</p>	<p>↓ Sertraline<sup>a</sup></p>	<p>Increases in sertraline dose should be guided by clinical response.</p>
<p>Antifungals: Voriconazole</p>	<p>↓ Voriconazole<sup>a</sup> ↑ efavirenz<sup>a</sup></p>	<p>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 capsule formulation.</p>

<p>Itraconazole</p> <p>Ketoconazole</p> <p>Posaconazole</p>	<p>↓ Itraconazole<sup>a</sup> ↓ Hydroxyitraconazole<sup>a</sup></p> <p>↓ Ketoconazole</p> <p>↓ posaconazole<sup>a</sup></p>	<p>Efavirenz tablet should not be broken.</p> <p>Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered.</p> <p>Drug interaction studies with efavirenz and ketoconazole have not been conducted. Efavirenz has the potential to decrease plasma concentrations of ketoconazole.</p> <p>Avoid concomitant use unless the benefit outweighs the risks.</p>
<p>Anti-infective: Clarithromycin</p>	<p>↓ Clarithromycin<sup>a</sup> ↑ 14-OH metabolite<sup>a</sup></p>	<p>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 <b>Other Drug following table</b>). Other macrolide antibiotics, such as erythromycin, have not been studied in combination with efavirenz.</p>
<p>Antimycobacterial Rifampin</p>	<p>↓ Efavirenz<sup>a</sup></p>	<p>Clinical significance of reduced efavirenz concentrations is unknown. Dosing</p>

Rifabutin	↓ Rifabutin <sup>a</sup>	<p>recommendations for concomitant use of efavirenz and rifampin have not been established.</p> <p>Increase daily dose of rifabutin by 50%. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week</p>
<p>Calcium channel blockers: Diltiazem</p> <p>Others (eg, felodipine, nicardipine, nifedipine, verapamil)</p>	<p>↓ Diltiazem <sup>a</sup> ↓ Desacetyl diltiazem <sup>a</sup> ↓ N-monodesmethyl diltiazem <sup>a</sup></p> <p>↓ Calcium channel blocker</p>	<p>Diltiazem dose adjustments should be guided by clinical response (refer to the full prescribing information for diltiazem). No dose adjustment of efavirenz is necessary when administered with diltiazem.</p> <p>No data are available on the potential interactions of efavirenz with other calcium channel blockers that are substrates of the CYP3A4 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).</p>
<p>HMG-CoA reductase inhibitors: Atorvastatin Pravastatin. Simvastatin</p>	<p>↓ Atorvastatin ↓ Pravastatin ↓ Simvastatin</p>	<p>Plasma concentrations of atorvastatin, pravastatin and simvastatin decreased. Consult the full prescribing information for the HMG-CoA reductase inhibitor for guidance on individualizing the dose.</p>

<p>Hormonal Contraceptives: Oral Ethinyl estradiol / Norgsetimate</p> <p>Implant Etonogestrel</p>	<p>↑ active metabolites of norgestimate<sup>a</sup></p> <p>↓ etonogestrel</p>	<p>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.</p> <p>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.</p>
<p>Immunosuppressants: Cyclosporine, tacrolimus, sirolimus and others metabolized by CYP3A</p>	<p>↓ Immunosuppressant</p>	<p>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</p>

		reached) is recommended when starting or stopping treatment with efavirenz.
Narcotic analgesic: Methadone	↓ Methadone <sup>a</sup>	Co-administration 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.

<sup>a</sup> See Tables 4 and 5 for magnitude of established interactions.

<sup>b</sup> This table is not all-inclusive.

### Other

### Drugs

Based on the results of drug interaction studies, 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.

### 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.

**Table 4: Effect of Efavirenz on Coadministered Drug Plasma C<sub>max</sub>, AUC and C<sub>min</sub>**

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	(mean % change)		
				C <sub>max</sub> (90% CI)	AUC (90% CI)	C <sub>min</sub> (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% <sup>a</sup> (↓ 17-↑ 58%)	↑ 39% <sup>a</sup> (2-88%)	↑ 48% <sup>a</sup> (24-76%)
	300 mg qd/ritonavir 100 mg qd d 1-10 (pm), then 400 mg qd/ritonavir 100 mg qd d 11-24 (pm) (simultaneous with efavirenz)	600 mg qd with a light snack d 11-24 (pm)	14	↑ 17% (8-27%)	↔	↓ 42% (31-51%)
Indinavir	1000 mg q8h x 10 days	600 mg qd x 10 days	20			
	After morning dose			↔ <sup>b</sup>	↓ 33% <sup>b</sup> (26-39%)	↓ 39% <sup>b</sup> (24-51%)
	After afternoon dose			↔ <sup>b</sup>	↓ 37% <sup>b</sup> (26-46%)	↓ 52% <sup>b</sup> (47-57%)
	After evening dose			↓ 29% <sup>b</sup> (11-43%)	↓ 46% <sup>b</sup> (37-54%)	↓ 57% <sup>b</sup> (50-63%)
Lopinavir/ritonavir	400/100 mg capsule q12h x 9 days	600 mg qd x 9 days	11,7 <sup>c</sup>	↔ <sup>d</sup>	↓ 19% <sup>d</sup> (↓ 36-↑ 3%)	↓ 39% <sup>d</sup> (3-62%)
	600/150 mg tablet q12h x 10 days with efavirenz compared to 400/100 mg q12h alone	600 mg qd x 9 days	23	↑ 36% <sup>d</sup> (28-44%)	↑ 36% <sup>d</sup> (28-44%)	↑ 32% <sup>d</sup> (21-44%)
Nelfinavir	750 mg q8h 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%)

Ritonavir	500 mg q12h x 8 days	600 mg qd x 10 days	11			
	After AM dose			↑ 24% (12-38%)	↑ 18% (6-33%)	↑ 42% (9-86%) <sup>e</sup>
	After PM dose			↔	↔	↑ 24% (3-50%) <sup>e</sup>
Saquinavir f SGC	1200 mg q8h x 10 days	600 mg qd x 10 days	12	↓ 50% (28-66%)	↓ 62% (45-74%)	↓ 56% (16-77%) <sup>e</sup>
Lamivudine	150 mg q12h x 14 days	600 mg qd x 14 days	9	↔	↔	↑ 265% (37-873%)
Tenofovir g	300 mg qd	600 mg qd x 14 days	29	↔	↔	↔
Zidovudine	300 mg q12h 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 single dose	400 mg qd x 7 days	14	↑ 22% (4-42%)	↔	NA
Clarithromycin	500 mg q12h 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 q12h x 28 days	600 mg qd x 14 days	18	↓ 37% (20-51%)	↓ 39% (21-53%)	↓ 44% (27-58%)
Hydroxy- itraconazole				↓ 35% (12-52%)	↓ 37% (14-55%)	↓ 43% (18-60%)
Posaconazole	400 mg (oral suspension) bid x 10 and 20 days	400 mg qd x 10 and 20 days	11	↓ 45% (34-53%)	↓ 50% (40-57%)	NA
Rifabutin	300 mg qd x 14 days	600 mg qd 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 qd x 9 days	NA	↓ 61% <sup>h</sup>	↓ 77% <sup>h</sup>	NA
	300 mg po q12h days 2-7	300 mg qd x 7 days	NA	↓ 36% <sup>i</sup> (21-49%)	↓ 55% <sup>i</sup> (45-62%)	NA
	400 mg po q12h days 2-7	300 mg qd x 7 days	NA	↑ 23% <sup>i</sup> (↓ 1-↑ 53%)	↓ 7% <sup>i</sup> (↓ 23-↑ 13%)	NA
Atorvastatin	10 mg qd x 4 days	600 mg qd 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 qd x 15 days	13	↓ 32% (↓ 59-↑ 12%)	↓ 44% (26-57%)	↓ 19% (0-35%)
Simvastatin	40 mg qd x 4 days	600 mg qd x 15 days	14	↓ 72% (63-79%)	↓ 68% (62-73%)	↓ 45% (20-62%)
Total active (including metabolites)				↓ 68% (55-78%)	↓ 60% (52-68%)	NA <sup>j</sup>
Carbamazepine	200 mg qd x 3 days, 200 mg bid 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-↑ 7%)
Cetirizine	10 mg single dose	600 mg qd x 10 days	11	↓ 24% (18-30%)	↔	NA
Diltiazem	240 mg x 21 days	600 mg qd 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-monodes- methyl diltiazem				↓ 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				
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 qd x 10 days	12	↑ 16% (2-32%)	↔	NA
Methadone	Stable maintenance 35-100 mg daily	600 mg qd x 14-21 days	11	↓ 45% (25-59%)	↓ 52% (33-66%)	NA
Paroxetine	20 mg qd x 14 days	600 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%)

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

<sup>a</sup> Compared with atazanavir 400 mg q.d. alone.

<sup>b</sup> Comparator dose of indinavir was 800 mg q8h × 10 days.

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

<sup>d</sup> Values are for lopinavir; the pharmacokinetics of ritonavir 100 mg q12h is unaffected by concurrent efavirenz.

<sup>e</sup> 95% CI.

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

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

<sup>h</sup> 95% CI not available

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

<sup>j</sup> Not available because of insufficient data.

NA = not available.

**Table 5: Effect of Co-administered Drug on Efavirenz Plasma C<sub>max</sub>, AUC and C<sub>min</sub>**

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Efavirenz (mean % change)		
				C <sub>max</sub> (90% CI)	AUC (90% CI)	C <sub>min</sub> (90% CI)
Indinavir	800 mg q8h x 14 days	200 mg qd x 14 days	11	↔	↔	↔
Lopinavir/ ritonavir	400/100 mg q12h x 9 days	600 mg qd x 9 days	11,12 <sup>a</sup>	↔	↓ 16% (↓ 38-↑ 15%)	↓ 16% (↓ 42-↑ 20%)
Nelfinavir	750 mg q8h x 7 days	600 mg qd x 7 days	10	↓ 12% (↓ 32-↑ 13%) <sup>b</sup>	↓ 12% (↓ 35-↑ 18%) <sup>b</sup>	↓ 21% (↓ 53-↑ 33%)
Ritonavir	500 mg q12h x 8 days	600 mg qd x 10 days	9	↑ 14% (4-26%)	↑ 21% (10-34%)	↑ 25% (7-46%) <sup>b</sup>
Saquinavir <sup>c</sup> SGC <sup>c</sup>	1200 mg q8h x 10 days	600 mg qd x 10 days	13	↓ 13% (5-20%)	↓ 12% (4-19%)	↓ 14% (2-24%) <sup>b</sup>
Tenofovir <sup>d</sup>	300 mg qd	600 mg qd x 14 days	30	↔	↔	↔
Azithromycin	600 mg single dose	400 mg qd x 7 days	14	↔	↔	↔
Clarithromycin	500 mg q12h x 7 days	400 mg qd 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 q12h x 14 days	600 mg qd x 28 days	16	↔	↔	↔
Rifabutin	300 mg qd x 14 days	600 mg qd x 14 days	11	↔	↔	↓ 12% (↓ 24-↑ 1%)
Rifampin	600 mg x 7 days	600 mg qd 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 qd x 9 days	NA	↑ 38% <sup>e</sup>	↑ 44% <sup>e</sup>	NA
	300 mg po q12h days 2-7	300 mg qd x 7 days	NA	↓ 14% <sup>f</sup> (7-21%)	↔ <sup>f</sup>	NA
	400 mg po q12h days 2-7	300 mg qd x 7 days	NA	↔ <sup>f</sup>	↑ 17% <sup>f</sup> (6-29%)	NA
Atorvastatin	10 mg qd x 4 days	600 mg qd x 15 days	14	↔	↔	↔

Pravastatin	40 mg qd x 4 days	600 mg qd x 15 days	11	↔	↔	↔
Simvastatin	40 mg qd x 4 days	600 mg qd x 15 days	14	↓ 12% (↓ 28-↑ 8%)	↔	↓ 12% (↓ 25-↑ 3%)
Aluminum hydroxide 400 mg, magnesium hydroxide 400 mg, plus simethicone 40 mg	30 mL single dose	400 mg single dose	17	↔	↔	NA
Carbamazepine	200 mg qd 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	400 mg single dose	17	↔	↔	NA
Paroxetine	20 mg qd x 14 days	600 mg qd x 14 days	12	↔	↔	↔
Sertraline	50 mg qd x 14 days	600 mg qd x 14 days	13	↑ 11% (6-16%)	↔	↔

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

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

<sup>b</sup> 95% CI.

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

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

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

<sup>f</sup> Relative to steady-state administration of efavirenz (600 mg once daily for 9 days).

NA = not available.

## 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.

## Co-administration with Related Products

Coadministration of efavirenz with combination of efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg is not recommended, since efavirenz is one of its active ingredients.

## 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%), non-fatal 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 a 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 **UNDESIRABLE EFFECTS**).

### **Nervous System Symptoms**

53%(531/1008) of patients receiving efavirenz reported central nervous system symptoms (any grade, regardless of causality) compared to 25% (156/635) of patients receiving control regimens. 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**). Dosing at bedtime may improve the tolerability of these nervous system symptoms (see **DOSAGE AND ADMINISTRATION**).

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.

### **Rash**

In controlled clinical trials, 26% (266/1008) of patients treated with 600 mg efavirenz experienced new-onset rash compared with 17% (111/635) of patients treated in control groups. Rash associated with blistering, moist desquamation or ulceration occurred in 0.9% of patients treated with efavirenz. The incidence of Grade 4 rash (eg, erythema multiforme or 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 **UNDESIRABLE EFFECTS**). One pediatric patient experienced Grade 3 rash (confluent rash with fever), and 2 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.

### **Hepatotoxicity**

Monitoring of liver enzymes before and during treatment is recommended for patients with underlying hepatic disease, including hepatitis B or C infection; patients with marked transaminase elevations; and patients treated with other medications associated with liver toxicity (see **UNDESIRABLE EFFECTS**). A few of the postmarketing reports of hepatic failure occurred in patients with no pre-existing hepatic disease or other identifiable risk factors (see **UNDESIRABLE EFFECTS**). Liver enzyme monitoring should also be considered for patients without pre-existing hepatic dysfunction or other risk factors. 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.

## **Convulsions**

Convulsions have been observed in patients receiving efavirenz, generally in the presence of known medical history of seizures. 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**).

## **Lipid Elevations**

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

## **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.

## **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.

## **Hepatic Impairment**

The pharmacokinetics of efavirenz has 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**).

## **Pregnancy**

### ***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 should 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.

### **Lactation**

**The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed 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 breastfeed if they are receiving efavirenz.**

### **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 AND UNDESIRABLE EFFECTS**).

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  $\mu\text{M}\cdot\text{h}$  (see **DOSAGE AND ADMINISTRATION**). The pharmacokinetics of efavirenz in pediatric patients was 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  $C_{\text{max}}$  was  $14.2 \pm 5.8 \mu\text{M}$  (mean  $\pm$  SD), steady-state  $C_{\text{min}}$  was  $5.6 \pm 4.1 \mu\text{M}$ , and AUC was  $218 \pm 104 \mu\text{M}\cdot\text{h}$ .

### **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.

## UNDESIRABLE EFFECTS

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

- psychiatric symptoms (see **WARNINGS AND PRECAUTIONS**)
- nervous system symptoms (see **WARNINGS AND PRECAUTIONS**)
- rash (see **WARNINGS AND PRECAUTIONS**)

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.

### 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  $\geq 2\%$  of efavirenz-treated patients in two controlled clinical trials are presented in Table 6.

**Table 6: Selected Treatment-Emergent <sup>a</sup> Adverse Reactions of Moderate or Severe Intensity Reported in  $\geq 2\%$  of Efavirenz-Treated Patients in Studies 006 and ACTG 364**

Adverse Reactions	Study 006			Study ACTG 364		
	LAM-, NNRTI-, and Protease Inhibitor-Naïve Patients			NRTI-Experienced, NNRTI-and Protease Inhibitor-Naïve Patients		
	Efavirenz <sup>b</sup> + ZDV/LAM  (n=412) 180 weeks <sup>c</sup>	Efavirenz <sup>b</sup> + Indinavir  (n=415) 102 weeks <sup>c</sup>	Indinavir + ZDV/LAM  (n=401) 76 weeks <sup>c</sup>	Efavirenz <sup>b</sup> + Nelfinavir + NRTIs  (n=64) 71.1 weeks <sup>c</sup>	Efavirenz + NRTIs  (n=65) 70.9 weeks <sup>c</sup>	Nelfinavir + NRTIs  (n=66) 62.7 weeks <sup>c</sup>
<b>Body as a Whole</b>						
Fatigue	8%	5%	9%	0	2%	3%
Pain	1%	2%	8%	13%	6%	17%
<b>Central and</b>						

<b>Peripheral Nervous System</b>						
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%
<b>Gastrointestinal</b>						
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%
<b>Psychiatric</b>						
Anxiety	2%	4%	<1%	–	–	–
Depression	5%	4%	<1%	3%	0	5%
Nervousness	2%	2%	0	2%	0	2%
<b>Skin and Appendages</b>						
Rash <sup>d</sup>	11%	16%	5%	9%	5%	9%
Pruritus	<1%	1%	1%	9%	5%	9%

<sup>a</sup> Includes adverse events at least possibly related to the study drug or of unknown relationship for Study 006. Includes all adverse events regardless of relationship to study drug for Study ACTG 364.

<sup>b</sup> Efavirenz provided as 600 mg once daily.

<sup>c</sup> Median duration of treatment.

<sup>d</sup> 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 **UNDESIRABLE EFFECTS, 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 7 lists the frequency of symptoms of different degrees of severity and gives the discontinuation rates in clinical trials for one or more of the following nervous system symptoms: dizziness, insomnia, impaired concentration, somnolence, abnormal dreaming, euphoria, confusion, agitation, amnesia, hallucinations, stupor, abnormal thinking, and depersonalization. (see **WARNINGS AND PRECAUTIONS**). The frequencies of specific central and peripheral nervous system symptoms are provided in Table 7.

**Table 7: Percent of Patients with One or More Selected Nervous System Symptoms<sup>a, b</sup>**

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

<sup>a</sup> Includes events reported regardless of causality.

<sup>b</sup> Data from Study 006 and three Phase 2/3 studies.

<sup>c</sup> “Mild” = Symptoms which do not interfere with a patient’s daily activities.

<sup>d</sup> “Moderate” = Symptoms which may interfere with daily activities

<sup>e</sup> “Severe” = Events which interrupt a 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 8 (see **WARNINGS AND PRECAUTIONS**).

**Table 8: Percent of Patients with Treatment-Emergent Rash** <sup>a, b</sup>

Percent of Patients with:	Description of Rash Grade <sup>c</sup>	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,	0.1	3.5	0.0

	necrosis requiring surgery, exfoliative dermatitis			
Treatment discontinuation as a result of rash	--	1.7	8.8	0.3

<sup>a</sup> Includes events reported regardless of causality.

<sup>b</sup> Data from Study 006 and three Phase 2/3 studies.

<sup>c</sup> NCI Grading System.

As seen in Table 8, rash is more common in pediatric patients and more often of higher grade (ie, more severe).(see **WARNINGS AND PRECAUTIONS**).

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. 9 of these patients developed mild – to - moderate rash while receiving therapy with efavirenz, and 2 of these patients discontinued because of rash.

### Laboratory Abnormalities

Selected Grade 3–4 laboratory abnormalities reported in  $\geq 2\%$  of efavirenz-treated patients in two clinical trials are presented in Table 9.

**Table 9: Selected Grade 3-4 Laboratory Abnormalites Reported in  $\geq 2\%$  of Efavirenz-treated Patients in Studies 006 and ACTG 364**

		Study 006 LAM -, NNRTI-, and Protease Inhibitor-Naive Patients			Study ACTG 364 NRTI-Experienced, NNRTI- and Protease Inhibitor-Naive Patients		
		Efavirenz <sup>a</sup> +ZDV/LAM (n=412)	Efavirenz <sup>a</sup> + Indinavir (n=415)	Indinavir + ZDV/ LAM (n=401)	Efavirenz <sup>a</sup> + Nelfinavir + NRTIs (n=64)	Efavirenz <sup>a</sup> + NRTIs (n=65)	Nelfinavir + NRTIs (n=66)
<b>Variable</b>	<b>Limit</b>	180 weeks <sup>b</sup>	102 weeks <sup>b</sup>	76 weeks <sup>b</sup>	71.1 weeks <sup>b</sup>	70.9 weeks <sup>b</sup>	62.7 weeks <sup>b</sup>

<b>Chemistry</b>							
ALT	>5 × ULN	5%	8%	5%	2%	6%	3%
AST	>5 × ULN	5%	6%	5%	6%	8%	8%
GGT <sup>c</sup>	>5 × ULN	8%	7%	3%	5%	0	5%
Amylase	>2 × ULN	4%	4%	1%	0	6%	2%
Glucose	>250 mg/dL	3%	3%	3%	5%	2%	3%
Triglycerides <sup>d</sup>	≥751 mg/dL	9%	6%	6%	11%	8%	17%
<b>Hematology</b>							
Neutrophils	<750/mm <sup>3</sup>	10%	3%	5%	2%	3%	2%

<sup>a</sup> Efavirenz provided as 600 mg once daily.

<sup>b</sup> Median duration of treatment.

<sup>c</sup> Isolated elevations of GGT in patients receiving efavirenz may reflect enzyme induction not associated with liver toxicity.

<sup>d</sup> 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 co-infected patients, elevations in AST to greater than five times the 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 the ULN developed in 20% of patients in the efavirenz arms and 7% of patients in the control arm. Among co-infected 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**).

### **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 non-fasting total cholesterol and high-density lipids (HDL) of approximately 20% and 25%, respectively, were observed. In patients treated with efavirenz + indinavir, increases from baseline in non-fasting cholesterol and HDL of approximately 40% and 35%, respectively, were observed. Non-fasting total cholesterol levels  $\geq 240$  mg/dL and  $\geq 300$  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**).

### **Clinical Trial Experience in Pediatric Patients**

Clinical adverse experiences observed in  $\geq 10\%$  of 57 pediatric patients aged 3 to 16 years who received efavirenz capsules, nelfinavir, and one or more NRTIs in Study ACTG 382 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 AND UNDESIRABLE EFFECTS**).

### **Observed During Clinical Practice**

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**).

**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. A few of the postmarketing reports of hepatic failure, including cases in patients with no pre-existing hepatic disease or other identifiable risk factors, were characterized by a fulminant course, progressing in some cases to transplantation or death.

**Metabolic and Nutritional:** Hypercholesterolemia, hypertriglyceridemia.

**Musculoskeletal:** Arthralgia, myalgia, myopathy.

**Psychiatric:** Aggressive reactions, agitation, delusions, emotional lability, mania, neurosis, paranoia, psychosis, suicide.

**Respiratory:** Dyspnea.

**Skin and Appendages:** Erythema multiforme, photoallergic dermatitis, skin discoloration, Stevens-Johnson syndrome.

**Special Senses:** Abnormal vision, tinnitus.

#### **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 efavirenz. 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.

#### **PACKAGING INFORMATION**

**EFAVIR-200 Capsules**.....Container of 30 capsules  
**EFAVIR-600 Tablets**.....Container of 30 tablets

*Last updated: October 2010*