For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

Efavirenz Capsules IP 200 mg
Efavirenz Tablets IP 600 mg

EFAVIR

COMPOSITION

EFAVIR-200 Capsules
Each hard gelatin capsule contains
Efavirenz IP ..... 200 mg
Colours: Brilliant Blue FCF, Sunset Yellow FCF and Titanium Dioxide IP

EFAVIR-600 Tablets
Each film-coated tablet contains
Efavirenz IP ..... 600 mg
Colours: Yellow Oxide of Iron & Titanium Dioxide IP

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 efavirenz.

Cardiac Electrophysiology

The effect of efavirenz on the QTc interval was evaluated in an open-label, positive and placebo controlled, fixed single sequence 3-period, 3-treatment crossover QT study in 58 healthy subjects enriched for CYP2B6 polymorphisms. The mean C_{max} of efavirenz in subjects with CYP2B6 *6/*6 genotype following the administration of 600 mg daily dose for 14 days was 2.25-fold the mean C_{max} observed in subjects with CYP2B6 *1/*1 genotype. A positive relationship between efavirenz concentration and QTc prolongation was observed. Based on the concentration-QTc relationship, the mean QTc prolongation and its upper bound 90% confidence interval are 8.7 ms and 11.3 ms in subjects with CYP2B6*6/*6 genotype following the administration of 600 mg daily dose for 14 days (see **WARNINGS AND PRECAUTIONS**).

Pharmacokinetics

Absorption: Peak efavirenz plasma concentrations of 1.6–9.1 µM were attained by 5 hours following single oral doses of 100 mg to 1600 mg administered to uninfected volunteers. Dose-related increases in C_{max} and AUC were seen for doses up to 1600 mg; the increases were less than proportional, suggesting diminished absorption at higher doses.

In HIV-1-infected patients at steady state, mean C_{max}, mean C_{min}, and mean AUC were dose proportional following 200 mg, 400 mg, and 600 mg daily doses. Time-to-peak plasma concentrations were approximately 3–5 hours and steady-state plasma concentrations were reached in 6–10 days. In 35 patients receiving 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 the AUC was 184 ± 73 µM•h.

Effect of Food on Oral Absorption

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

Tablets: Administration of a single 600 mg efavirenz tablet with a high-fat/high-caloric meal (approximately 1000 kcal, 500–600 kcal from fat) was associated with a 28% increase in mean AUC_∞ of efavirenz and a 79% increase in mean C_{max} of efavirenz relative to the exposures achieved under fasted conditions (see **DOSAGE AND ADMINISTRATION**).

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

Distribution: Efavirenz is highly bound (approximately 99.5–99.75%) to human plasma proteins, predominantly albumin. In HIV-1 infected patients (n=9) who received efavirenz 200 to 600 mg once daily for at least one month, cerebrospinal fluid concentrations ranged from 0.26% to 1.19% (mean: 0.69%) of the corresponding plasma concentration. This proportion is approximately 3-fold higher than the non-protein-bound (free) fraction of efavirenz in plasma.

Metabolism: Studies in humans and *in vitro* studies using human liver microsomes have demonstrated that efavirenz is principally metabolized by the cytochrome P450 system to hydroxylated metabolites, with subsequent glucuronidation of these hydroxylated metabolites. These metabolites are essentially inactive against HIV-1. The *in vitro* studies suggest that CYP3A and CYP2B6 are the major isozymes responsible for efavirenz metabolism.

Efavirenz has been shown to induce CYP enzymes, resulting in the induction of its own metabolism. Multiple doses of 200–400 mg per day for 10 days resulted in a lower than predicted extent of accumulation (22–42% lower) and a shorter terminal half-life of 40–55 hours (single dose half-life: 52–76 hours).

Elimination: Efavirenz has a terminal half-life of 52–76 hours after single doses and 40–55 hours after multiple doses. A one-month mass balance/excretion study was conducted using 400 mg per day with a ^{14}C-labeled dose administered on Day 8. Approximately 14–34% of the radiolabel was recovered in the urine and 16–61% was recovered in the feces. Nearly all of the urinary excretion of the radiolabeled drug was in the form of metabolites. Efavirenz accounted for the majority of the total radioactivity measured in the 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 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.

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

INDICATIONS

EFAVIR Capsules and Tablets are indicated for the treatment of HIV-1infection in combination with other antiretroviral agents.

DOSAGE AND ADMINISTRATION

Hepatic Function

Monitor hepatic function prior to and during treatment with EFAVIR (see **WARNINGS AND PRECAUTIONS**). EFAVIR is not recommended in patients with moderate or severe hepatic impairment (Child Pugh B or C) (see **WARNINGS AND PRECAUTIONS and USE IN SPECIFIC POPULATIONS**).

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 to

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**). **EFAVIR** capsules or tablets should be swallowed intact with liquid (see **DOSAGE AND ADMINISTRATION**).

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 capsule formulation (one 200-mg and two 50-mg capsules or six 50-mg capsules). Efavirenz tablet should not be broken (see **WARNINGS AND PRECAUTIONS- Drug Interactions and PHARMACOLOGY**).

If **EFAVIR** is coadministered with rifampin to patients weighing 50 kg or more, an increase in the dose of **EFAVIR** to 800 mg once daily is recommended (see **WARNINGS AND PRECAUTIONS- Drug Interactions and PHARMACOLOGY**).

CONTRAINDICATIONS

- **EFAVIR Capsules and Tablets** is contraindicated in patients with previously demonstrated clinically significant hypersensitivity (eg, Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the components of this product.
- Coadministration of efavirenz with elbasvir and grazoprevir is contraindicated (see **WARNINGS AND PRECAUTIONS-Drug Interactions**).

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 or CYP2B6. The most prominent effect of efavirenz at steady-state is induction of CYP3A and CYP2B6 (see **DOSAGE AND ADMINISTRATION and WARNING AND PRECAUTIONS-Drug Interactions**).

Potential for EFAVIRENZ to Affect other Drugs

Efavirenz has been shown in vivo to induce CYP3A and CYP2B6. Other compounds that are substrates of CYP3A or CYP2B6 may have decreased plasma concentrations when coadministered with efavirenz.

Potential for Other Drugs to Affect EFAVIRENZ

Drugs that induce CYP3A activity (eg, phenobarbital, rifampin, rifabutin) would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations (see **DOSAGE AND ADMINISTRATION**).

QT Prolonging Drugs

There is limited information available on the potential for a pharmacodynamic interaction between efavirenz and drugs that prolong the QTc interval. QTc prolongation has been observed with the use of efavirenz (see **PHARMACOLOGY**). Consider alternatives to efavirenz when coadministered with a drug with a known risk of Torsade de Pointes.

Established and Other Potentially Significant Drug Interactions

Drug interactions with efavirenz are summarized in Table 1. This table includes potentially significant interactions, but is not all inclusive.

Table 1: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect	Clinical Comment
HIV antiretroviral agents		
Protease inhibitor: Fosamprenavir calcium	↓ amprenavir	Fosamprenavir (unboosted): Appropriate doses of the combinations with respect to safety and efficacy have not been established. Fosamprenavir/ritonavir: An additional 100 mg/day (300 mg total) of ritonavir is recommended when efavirenz is administered with fosamprenavir/ritonavir once daily. No change in the ritonavir dose is required when efavirenz is administered with fosamprenavir plus ritonavir twice daily.
Protease inhibitor: Atazanavir	↓ atazanavir*	*Treatment naïve patients:* When coadministered with efavirenz, the recommended dose of atazanavir is 400 mg with ritonavir 100 mg (together once daily with food) and efavirenz 600 mg (once daily on an empty stomach, preferably at bedtime). *Treatment-experienced patients:* Coadministration of efavirenz and atazanavir is not recommended.
Protease inhibitor: Indinavir	↓ indinavir*	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.
Protease inhibitor: Lopinavir/ritonavir	↓ Lopinavir*	Lopinavir/ritonavir once daily dosing is not recommended when coadministered with efavirenz. The dose of lopinavir/ritonavir must be increased when coadministered with efavirenz. See the lopinavir/ritonavir prescribing information for dose adjustments of lopinavir/ritonavir when coadministered with efavirenz in adult and pediatric patients.
Protease inhibitor: Ritonavir	↑ ritonavir* ↑ efavirenz*	Monitor for elevation of liver enzymes and for adverse clinical experiences (e.g., dizziness, nausea, paresthesia) when efavirenz is coadministered with ritonavir. .
Protease inhibitor: Saquinavir	↓ saquinavir*	Appropriate doses of the combination of efavirenz and saquinavir/ritonavir with respect to safety and efficacy have not been established.
NNRTI: Other NNRTIs	↑ or ↓ efavirenz and/or NNRTI	Combining two NNRTIs has not been shown to be beneficial. Efavirenz should not be coadministered with other NNRTIs.
CCR5 co-receptor antagonist: Maraviroc	↓ maraviroc*	Refer to the full prescribing information for maraviroc for guidance on coadministration with efavirenz.
Hepatitis C antiviral agents		
Boceprevir	↓ boceprevir*	Concomitant administration of boceprevir with efavirenz is not recommended because it may result in loss of therapeutic effect of boceprevir. .
Simeprevir	↓ simeprevir* ↔ efavirenz*	Concomitant administration of simeprevir and efavirenz is not recommended because it may result in loss of therapeutic effect of simeprevir.
Elbasvir/Grazoprevir	↓ elbasvir ↓ grazoprevir	Coadministration of efavirenz with elbasvir/grazoprevir is contraindicated (*see Contraindications)* because it may lead to loss of virologic response to elbasvir/grazoprevir.

Pibrentasvir/Glecaprevir	↓ pibrentasvir ↓ glecaprevir	Coadministration of efavirenz is not recommended because it may lead to reduced therapeutic effect of pibrentasvir/glecaprevir.
Velpatasvir/ Sofosbuvir	↓ velpatasvir	Coadministration of efavirenz and sofosbuvir/velpatasvir is not recommended because it may result in loss of therapeutic effect of sofosbuvir/velpatasvir.
Velpatasvir /Sofosbuvir/ / Voxilaprevir	↓ velpatasvir ↓ voxilaprevir	Coadministration of efavirenz and sofosbuvir/velpatasvir/ voxilaprevir is not recommended because it may result in loss of therapeutic effect of sofosbuvir/velpatasvir/ voxilaprevir.
Other agents		
Anticoagulant: Warfarin	↑ or ↓ Warfarin	Monitor INR and adjust warfarin dosage if necessary..
Anticonvulsants: Carbamazepine	↓ carbamazepine* ↓ efavirenz*	There are insufficient data to make a dose recommendation for efavirenz. Alternative anticonvulsant treatment should be used.
Phenytoin Phenobarbital	↓ anticonvulsant ↓ efavirenz	Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.
Antidepressants: Bupropion	↓ bupropion*	Increases in bupropion dosage should be guided by clinical response, Bupropion dose should not exceed the maximum recommended dose.
Sertraline	↓ sertraline*	Increases in sertraline dose should be guided by clinical response.
Antifungals: Voriconazole	↓voriconazole* ↑efavirenz*	Efavirenz and voriconazole should not be coadministered at standard doses. 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. Efavirenz tablet should not be broken (See **DOSAGE AND ADMINISTRATION**).
Itraconazole	↓ itraconazole* ↓hydroxyitraconazole*	Consider alternative antifungal treatment because no dose recommendation for itraconazole can be made.
Ketoconazole Posaconazole	↓ ketoconazole* ↓ posaconazole*	Consider alternative antifungal treatment because no dose recommendation for ketonazole can be made. Avoid concomitant use unless the benefit outweighs the risks.
Anti-infective: Clarithromycin	↓ clarithromycin* ↑ 14-OH metabolite*	Consider alternatives to macrolide antibiotics because of the risk of QT interval prolongation
Antimycobacterial Rifabutin	↓ rifabutin*	Increase daily dose of rifabutin by 50%. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week.
Rifampin	↓ efavirenz*	Increase efavirenz to 800 mg once daily when coadministered with rifampin to patients weighing 50 kg or more.
Antimalarials: Artemether/ Lumefantrine	↓ artemether* ↓ dihydroartemisinin* ↓ lumefantrine*	Consider alternatives to artemether/ lumefantrine because of the risk of QT interval prolongation.
Atovaquone/ proguanil	↓ atovaquone ↓ proguanil	Concomitant administration is not recommended
Calcium channel blockers: Diltiazem	↓ diltiazem* ↓ desacetyl diltiazem* ↓ N-monodesmethyl diltiazem*	Diltiazem dose adjustments should be guided by clinical response (refer to the full prescribing information for diltiazem). No dose adjustment of efavirenz is necessary when administered with diltiazem.
Others (eg, felodipine, nicardipine, nifedipine, verapamil)	↓ calcium channel blocker	When coadministered with efavirenz, dosage adjustment of calcium channels blocker may be needed and should be guided by clinical response (refer to the full prescribing information for the calcium channel blocker).
HMG-CoA reductase inhibitors: Atorvastatin Pravastatin Simvastatin	↓ atorvastatin* ↓ pravastatin* ↓ simvastatin*	Plasma concentrations of atorvastatin, pravastatin and simvastatin decreased. Consult the full prescribing information for the HMG-CoA reductase inhibitor for guidance on individualizing the dose.
Hormonal contraceptives: Oral Ethinyl estradiol/ Norgsetimate	↓ active metabolites of norgestimate*	A reliable method of barrier contraception must be used in addition to hormonal contraceptives.
Implant Etonogestrel	↓ etonogestrel	A reliable method of barrier contraception must be used in addition to hormonal contraceptives. The interaction between etonogestrel and efavirenz has not been studied. Decreased exposure of etonogestrel may be expected. There have been postmarketing reports of contraceptive failure with etonogestrel in efavirenz-exposed patients.
Immunosuppressants: Cyclosporine, tacrolimus, sirolimus and others metabolized by CYP3A	↓ immunosuppressant	Dose adjustments of the immunosuppressant may be required. Close monitoring of immunosuppressant concentrations for at least 2 weeks (until stable concentrations are reached) is recommended when starting or stopping treatment with efavirenz.
Narcotic analgesic: Methadone	↓ methadone*	Monitor for signs of methadone withdrawal and increase methadone dose if required to alleviate withdrawal symptoms.

*The interaction between efavirenz and the drug was evaluated in a clinical study. All other drug interactions shown are predicted.
This table is not all-inclusive.

Drugs Without Clinically Significant Interactions with Efavirenz
No dosage adjustment is recommended when efavirenz is given with the following: aluminum/magnesium

hydroxide antacids, azithromycin, cetirizine, famotidine, fluconazole, lamivudine, lorazepam, nelfinavir, paroxetine, nucleoside reverse transcriptase inhibitors (abacavir, emtricitabine, lamivudine, stavudine, tenofovir disoproxil fumarate, and zidovudine) and raltegravir.

Cannabinoid Test Interaction

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

QTc Prolongation

QTc prolongation has been observed with the use of efavirenz (see **WARNINGS AND PRECAUTIONS- Drug Interactions AND PHARMACOLOGY**) Consider alternatives to efavirenz when coadministered with a drug with a known risk of Torsade de Pointes or when administered to patients at higher risk of Torsade de Pointes.

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 unless needed for dose adjustment (eg, with rifampin), 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 Postmarketing cases of catatonia have also been reported and may be associated with increased efavirenz exposure. 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

Fifty-three percent (531/1008) of patients receiving efavirenz in controlled trials reported central nervous system symptoms (any grade, regardless of causality) compared to 25% (156/635) of patients receiving control regimens (see **UNDESIRABLE EFFECTS**). 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.

Embryo-Fetal Toxicity

Efavirenz may cause fetal harm when administered during the first trimester to a pregnant woman. Advise females of reproductive potential who are receiving efavirenz to avoid pregnancy.

Rash

In controlled clinical trials, 26% (266/1008) of adult patients treated with 600 mg efavirenz experienced new-onset skin rash compared with 17% (111/635) of those treated in control groups (see **UNDESIRABLE EFFECTS**). Rash associated with blistering, moist desquamation or ulceration occurred in 0.9% (9/1008) of patients treated with efavirenz. The incidence of Grade 4 rash (eg, erythema multiforme or Stevens-Johnson syndrome) in adult 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).

Rash was reported in 59 of 182 pediatric patients (32%) treated with efavirenz (see **UNDESIRABLE EFFECTS**). Two pediatric patients experienced Grade 3 rash (confluent rash with fever, generalized rash), and four patients had Grade 4 rash (erythema multiforme). The median time to onset of rash in pediatric patients was 28 days (range 3-1642 days). Prophylaxis with appropriate antihistamines before initiating therapy with efavirenz in pediatric patients should be considered.

Efavirenz can generally 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. For patients who have had a life-threatening cutaneous reaction (eg, Stevens-Johnson syndrome), alternative therapy should be considered (see **CONTRAINDICATIONS**).

Hepatotoxicity

Postmarketing cases of hepatitis, including fulminant hepatitis progressing to liver failure requiring transplantation or resulting in death, have been reported in patients treated with efavirenz. Reports have included patients with underlying hepatic disease, including coinfection with hepatitis B or C, and patients without pre-existing hepatic disease or other identifiable risk factors.

Efavirenz is not recommended for patients with moderate or severe hepatic impairment. Careful monitoring is recommended for patients with mild hepatic impairment receiving efavirenz (see **UNDESIRABLE EFFECTS and USE IN SPECIFIC POPULATIONS**).

Monitoring of liver enzymes before and during treatment is recommended for all patients (see **DOSAGE AND ADMINISTRATION**). Consider discontinuing efavirenz in patients with persistent elevations of serum transaminases to greater than five times the upper limit of the normal range.

Discontinue efavirenz if elevation of serum transaminases is accompanied by clinical signs or symptoms of hepatitis or hepatic decompensation.

Convulsions

Convulsions have been observed in adult and pediatric 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 **WARNINGS AND PRECAUTIONS- 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.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of 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.

Pregnancy

Risk Summary

There are retrospective case reports of neural tube defects in infants whose mothers were exposed to efavirenz-containing regimens in the first trimester of pregnancy. Prospective pregnancy data from the Antiretroviral Pregnancy Registry are not sufficient to adequately assess this risk. Available data from the Antiretroviral Pregnancy Registry show no difference in the risk of overall major birth defects compared to the background rate for major birth defects of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). Although a causal relationship has not been established between exposure to efavirenz in the first trimester and neural tube defects, similar malformations have been observed in studies conducted in monkeys at doses similar to the human dose. In addition, fetal and embryonic toxicities occurred in rats, at a dose ten times less than the human exposure at recommended clinical dose. Because of the potential risk of neural tube defects, efavirenz should not be used in the first trimester of pregnancy. Advise pregnant women of the potential risk to a fetus.

Data

Human Data

There are retrospective postmarketing reports of findings consistent with neural tube defects, including meningomyelocele, all in infants of mothers exposed to efavirenz-containing regimens in the first trimester.

Based on prospective reports from the Antiretroviral Pregnancy Registry (APR) of approximately 1000 live births following exposure to efavirenz-containing regimens (including Reference ID: 3979875 18 over 800 live births exposed in the first trimester), there was no difference between efavirenz and overall birth defects compared with the background birth defect rate of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program. As of the interim APR report issued December 2014, the prevalence of birth defects following first-trimester exposure was 2.3% (95% CI: 1.4%-3.6%). One of these prospectively reported defects with first trimester exposure was a neural tube defect. A single case of anophthalmia with first-trimester exposure to efavirenz has also been prospectively reported. This case also included severe oblique facial clefts and amniotic banding, which have a known association with anophthalmia.

Animal Data

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

Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Because of the potential for HIV transmission in breastfed infants, advise mothers not to breastfeed.

Females and Males of Reproductive Potential

Because of potential teratogenic effects, pregnancy should be avoided in women receiving efavirenz (see **USE IN SPECIFIC POPULATIONS**).

Pregnancy Testing

Females of reproductive potential should undergo pregnancy testing before initiation of efavirenz

Contraception

Females of reproductive potential should use effective contraception during treatment with efavirenz and for 12 weeks after discontinuing EFAVIRENZ due to the long half-life of efavirenz. Barrier contraception should always be used in combination with other methods of contraception. Hormonal methods that contain progesterone may have decreased effectiveness (see **WARNINGS AND PRECAUTIONS- Drug Interactions**).

Pediatric Use

The safety, pharmacokinetic profile, and virologic and immunologic responses of efavirenz were evaluated in antiretroviral-naive and -experienced HIV-1 infected pediatric patients 3 months to 21 years of age in three open-label clinical trials (see **UNDESIRABLE EFFECTS**). The type and frequency of adverse reactions in these trials were generally similar to those of adult patients with the exception of a higher frequency of rash, including a higher frequency of Grade 3 or 4 rash, in pediatric patients compared to adults (see **WARNINGS AND PRECAUTIONS** and **UNDESIRABLE EFFECTS**).

Use of efavirenz in patients younger than 3 months of age OR less than 3.5 kg body weight is not recommended because the safety, pharmacokinetics, and antiviral activity of efavirenz have not been evaluated in this age group and there is a risk of developing HIV resistance if efavirenz is underdosed.

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.

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 AND PHARMACOLOGY**).

UNDESIRABLE EFFECTS

The most significant adverse reactions 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**)
- hepatotoxicity (see **WARNINGS AND PRECAUTIONS**)

Clinical Trials Experience

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.

Adverse Reactions in Adults

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.

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

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

Adverse Reactions	Study 006 LAM-, NNRTI-, and Protease Inhibitor-Naïve Patients			Study ACTG 364 NRTI-Experienced, NNRTI-and Protease Inhibitor-Naïve Patients		
	Efavirenz[b] + ZDV/LAM (n=412) 180 weeks[c]	Efavirenz[b] + Indinavir (n-415) 102 weeks[c]	Indinavir + ZDV/LAM (n=401) 76 weeks[c]	Efavirenz[b] + Nelfinavir + NRTIs (n=64) 71.1 weeks[c]	Efavirenz + NRTIs (n=65) 70.9 weeks[c]	Nelfinavir + NRTIs (n=66) 62.7 weeks[c]
Body as a Whole						
Fatigue	8%	5%	9%	0	2%	3%
Pain	1%	2%	8%	13%	6%	17%
Central and Peripheral Nervous System						
Dizziness	9%	9%	2%	2%	6%	6%
Headache	8%	5%	3%	5%	2%	3%
Insomnia	7%	7%	2%	0	0	2%
Concentration impaired	5%	3%	<1%	0	0	0
Abnormal dreams	3%	1%	0	–	–	–
Somnolence	2%	2%	<1%	0	0	0
Anorexia	1%	<1%	<1%	0	2%	2%
Gastrointestinal						
Nausea	10%	6%	24%	3%	2%	2%
Vomiting	6%	3%	14%	–	–	–
Diarrhea	3%	5%	6%	14%	3%	9%
Dyspepsia	4%	4%	6%	0	0	2%
Abdominal pain	2%	2%	5%	3%	3%	3%
Psychiatric						
Anxiety	2%	4%	<1%	–	–	–
Depression	5%	4%	<1%	3%	0	5%
Nervousness	2%	2%	0	2%	0	2%
Skin and Appendages						
Rash[d]	11%	16%	5%	9%	5%	9%
Pruritus	<1%	1%	1%	9%	5%	9%

[a] Includes adverse events at least possibly related to the study drug or of unknown relationship for Study 006. Includes all adverse events regardless of relationship to study drug for Study ACTG 364.
[b] Efavirenz provided as 600 mg once daily.
[c] Median duration of treatment.
[d] Includes erythema multiforme, rash, rash erythematous, rash follicular, rash maculopapular, rash petechial, rash pustular, and urticaria for Study 006 and macules, papules, rash, erythema, redness, inflammation, allergic rash, urticaria, welts, hives, itchy, and pruritus for ACTG 364.
– = Not Specified.
ZDV = Zidovudine; LAM = Lamivudine

Pancreatitis has been reported, although a causal relationship with efavirenz has not been established. Asymptomatic increases in serum amylase levels were observed in a significantly higher number of patients treated with efavirenz 600 mg than in control patients (see **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 5 lists the frequency of symptoms of different degrees of severity and gives the discontinuation rates for one or more of the following nervous system symptoms: dizziness, insomnia, impaired concentration, somnolence, abnormal dreaming, euphoria, confusion, agitation, amnesia, hallucinations, stupor, abnormal thinking, and depersonalization (see **WARNINGS AND PRECAUTIONS**).The frequencies of specific central and peripheral nervous system symptoms are provided in Table 3.

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

Percent of Patients with:	Efavirenz 600 mg Once Daily (n=1008) %	Control Groups (n=635) %
Symptoms of any severity	52.7	24.6

Mild symptoms[c]	33.3	15.6
Moderate symptoms[d]	17.4	7.7
Severe symptoms[e]	2.0	1.3
Treatment discontinuation as a result of symptoms	2.1	1.1

[a] Includes events reported regardless of causality.
[b] Data from Study 006 and three Phase 2/3 studies.
[c] "Mild" = Symptoms which do not interfere with a patient's daily activities.
[d] "Moderate" = Symptoms which may interfere with daily activities
[e] "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 greater than 2% among patients treated with efavirenz or control regimens, respectively, were depression (19%, 16%), anxiety (13%, 9%) and nervousness (7%, 2%).

Rash
In controlled clinical trials, the frequency of rash (all grades, regardless of causality) was 26% for 1008 adults treated with regimens containing efavirenz and 17% for 635 adults treated with a control regimen. Most reports of rash were mild or moderate in severity. The frequency of Grade 3 rash was 0.8% for efavirenz-treated patients and 0.3% for control groups, and the frequency of Grade 4 rash was 0.1% for efavirenz and 0 for control groups. The discontinuation rates as a result of rash were 1.7% for efavirenz-treated patients and 0.3% for control groups (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. Nine of these patients developed mild-to-moderate rash while receiving therapy with efavirenz, and two of these patients discontinued because of rash.

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

Table 4: Selected Grade 3-4 Laboratory Abnormalites Reported in ≥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[a] +ZDV/LAM (n=412)	Efavirenz[a] + Indinavir (n=415)	Indinavir + ZDV/ LAM (n=401)	Efavirenz[a] + Nelfinavir + NRTIs (n=64)	Efavirenz[a] + NRTIs (n=65)	Nelfinavir + NRTIs (n=66)
Variable	**Limit**	**180 weeks[b]**	**102 weeks[b]**	**76 weeks[b]**	**71.1 weeks[b]**	**70.9 weeks[b]**	**62.7 weeks[b]**
Chemistry							
ALT	>5 × ULN	5%	8%	5%	2%	6%	3%
AST	>5 × ULN	5%	6%	5%	6%	8%	8%
GGT[c]	>5 × ULN	8%	7%	3%	5%	0	5%
Amylase	>2 × ULN	4%	4%	1%	0	6%	2%
Glucose	>250 mg/dL	3%	3%	3%	5%	2%	3%
Triglycerides[d]	≥751 mg/dL	9%	6%	6%	11%	8%	17%
Hematology							
Neutrophils	<750/mm³	10%	3%	5%	2%	3%	2%

Efavirenz provided as 600 mg once daily.
Median duration of treatment.
Isolated elevations of GGT in patients receiving efavirenz may reflect enzyme induction not associated with ver toxicity.
Nonfasting.
DV = Zidovudine, LAM = Lamivudine, ULN = Upper limit of normal, ALT = Alanine aminotransferase, AST = spartate aminotransferase, GGT = Gamma-glutamyltransferase

'atients Coinfected with Hepatitis B or C
iver function tests should be monitored in patients with a history of hepatitis B and/or C. In the long-term data et from Study 006, 137 patients treated with efavirenz-containing regimens (median duration of therapy, 68 eeks) and 84 treated with a control regimen (median duration, 56 weeks) were seropositive at screening for epatitis B (surface antigen positive) and/or C (hepatitis C antibody positive). Among these co-infected patients, 'evations in AST to greater than five times the ULN developed in 13% of patients in the efavirenz arms and 7% f those in the control arm, and elevations in ALT to greater than five times the ULN developed in 20% of patients the efavirenz arms and 7% of patients in the control arm. Among co-infected patients, 3% of those treated with 'avirenz-containing regimens and 2% in the control arm discontinued from the study because of liver or biliary ystem disorders (see **WARNINGS AND PRECAUTIONS**).

ipids
creases from baseline in total cholesterol of 10–20% have been observed in some uninfected volunteers ceiving efavirenz. In patients treated with efavirenz + zidovudine + lamivudine, increases from baseline in on-fasting total cholesterol and high-density lipids (HDL) of approximately 20% and 25%, respectively, were bserved. In patients treated with efavirenz + indinavir, increases from baseline in non-fasting cholesterol and DL of approximately 40% and 35%, respectively, were observed. Non-fasting total cholesterol levels ≥240 mg/ . and ≥300 mg/dL were reported in 34% and 9%, respectively, of patients treated with efavirenz + zidovudine lamivudine; 54% and 20%, respectively, of patients treated with efavirenz + indinavir; and 28% and 4%, spectively, of patients treated with indinavir + zidovudine + lamivudine. The effects of efavirenz on triglycerides id LDL in this study were not well characterized since samples were taken from nonfasting patients. The clinical gnificance of these findings is unknown (see **WARNINGS AND PRECAUTIONS**).

ostmarketing Experience
ne following adverse reactions have been identified during post approval use of efavirenz. Because these actions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate eir frequency or establish a causal relationship to drug exposure.

ody as a Whole: allergic reactions, asthenia, redistribution/accumulation of body fat (see **WARNINGS AND RECAUTIONS**)

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

ndocrine: gynecomastia

astrointestinal: constipation, malabsorption

rdiovascular: flushing, palpitations

ver and Biliary System: hepatic enzyme increase, hepatic failure, hepatitis.

etabolic and Nutritional: hypercholesterolemia, hypertriglyceridemia

usculoskeletal: arthralgia, myalgia, myopathy

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

Respiratory: dyspnea

Skin and Appendages: erythema multiforme, photoallergic dermatitis, Stevens-Johnson syndrome

Special Senses: abnormal vision, tinnitus

If you experience any side effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 30

By reporting side effects, you can help provide more information on the safety of this product.

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

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

SHELF-LIFE: See on Pack

STORAGE AND HANDLING INSTRUCTIONS: Store in a cool dry place, away from moisture.

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

Last updated: **January 20**
Last reviewed: **January 20**

Cipla

21069820
BP4