

# Efavirenz

**Brand Name:** Sustiva

**Drug Class:** Non-nucleoside Reverse Transcriptase Inhibitors

## Drug Description

Efavirenz, also known as EFV, is a benzoxazinone derivative non-nucleoside reverse transcriptase inhibitor (NNRTI). [1]

## HIV/AIDS-Related Uses

Efavirenz was approved by the FDA on September 17, 1998, for use in combination with other antiretroviral agents for the treatment of HIV-1 infection.[2] Efavirenz was approved under the FDA's accelerated review process, which allows approval based on analysis of surrogate markers or response, such as T-cell counts and HIV RNA viral levels, rather than clinical endpoints such as disease progression or survival.[3] The safety and efficacy of efavirenz in children less than 3 years of age have not been established.[4]

Efavirenz, in combination with either zidovudine and lamivudine or emtricitabine and tenofovir disoproxil fumarate, is part of two of the preferred regimens for treatment-naïve patients.[5]

Efavirenz may be used with other antiretroviral agents as part of an expanded postexposure prophylaxis regimen for health care workers and other individuals exposed occupationally to tissues, blood, or other body fluids associated with a high risk for HIV transmission.[6]

## Pharmacology

Efavirenz is a noncompetitive inhibitor of HIV-1 reverse transcriptase (RT). It has no inhibitory effect on HIV-2 RT or human cellular DNA polymerases alpha, beta, gamma, or delta.[7] Efavirenz binds directly to RT and inhibits viral RNA- and DNA-dependent DNA polymerase activities by disrupting the catalytic site. Although the drug-RT-template complex may continue to bind deoxynucleoside triphosphate and to catalyze its incorporation into the newly forming viral DNA, it does so at a slower rate.[8]

Following oral administration of a single 100 mg to 1,600 mg dose of efavirenz in healthy adults, peak plasma drug concentrations (C<sub>max</sub>) of 0.51 to 2.9

mcg/ml were attained within 5 hours. Increases in C<sub>max</sub> and area under the plasma concentration-time curve (AUC) were dose proportional for 200, 400, and 600 mg efavirenz doses; the increases were less than proportional for a 1,600 mg efavirenz dose, suggesting reduced absorption at higher doses. Times to peak plasma concentrations were approximately 3 to 5 hours, and steady-state plasma concentrations were reached in 6 to 10 days. Following oral administration of a single 400 mg efavirenz dose in individuals with chronic liver disease or healthy individuals, C<sub>max</sub> averaged 1.2 or 1.8 mcg/ml, respectively, and AUC averaged 94.4 or 96.3 (hr)mcg/ml.[9]

Normal meals had no significant effect on the bioavailability of 100 mg of efavirenz administered twice a day for 10 days. The relative bioavailability of a single 1,200 mg dose of efavirenz in uninfected volunteers was increased by 50% following a high fat meal.[10]

Distribution of efavirenz into body tissues and fluids has not been fully characterized. In animal models, efavirenz's volume of distribution following IV administration suggests extensive tissue distribution. In HIV infected patients who received 200 mg to 600 mg of efavirenz once a day for at least 1 month, cerebrospinal fluid concentrations ranged from 0.26% to 1.19% of the corresponding plasma concentration. This proportion is approximately threefold higher than the nonprotein-bound (free) fraction of efavirenz in plasma. Efavirenz is highly bound (approximately 99.5% to 99.75%) to human plasma proteins, principally albumin.[11]

Efavirenz is in FDA Pregnancy Category D. Efavirenz may cause fetal harm when administered during the first trimester of pregnancy. No adequate and well-controlled studies have been performed in pregnant women.[12] In prospective reports, birth defects have occurred in 5 of 228 live births after first trimester maternal exposure; none were neural tube defects. Four retrospective reports identified findings consistent with neural tube defects, including meningocele, in mothers exposed to efavirenz during the mother's first trimester.

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## Pharmacology (cont.)

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Although a causal relationship has not been established, similar defects have been observed in preclinical studies of efavirenz.[13]

Two methods of birth control, with a barrier method in combination with a nonbarrier method such as an oral or other hormonal contraceptive, should be used to avoid pregnancy in women taking efavirenz. Before initiating therapy with efavirenz, women of childbearing potential should undergo pregnancy testing. It is recommended that efavirenz not be given to pregnant women except in situations in which there are no therapeutic alternatives. An Antiretroviral Pregnancy Registry has been established to monitor the outcomes of pregnant women exposed to efavirenz. Physicians may register patients online at <http://www.APRegistry.com> or by calling 1-800-258-4263. It is not known whether efavirenz is distributed into breast milk in humans; however, efavirenz is distributed into the milk of laboratory animals. Breastfeeding is not recommended during efavirenz therapy.[14]

Efavirenz is metabolized primarily by the hepatic cytochrome P450 (CYP) isoenzymes 3A4 and 2B6 into hydroxylated, inactive metabolites. These metabolites undergo subsequent glucuronidation. Ten days of therapy with 200 mg to 400 mg of efavirenz daily resulted in a lower than expected accumulation of medication (22% to 42% lower) and a shorter terminal half-life (40 to 55 hours) compared to the single-dose half-life (52 to 76 hours).[15]

Efavirenz appears to induce its own metabolism. Terminal elimination half-life is prolonged in patients with chronic liver disease. Following oral administration of a single 400 mg dose of efavirenz, a half-life of 152 or 118 hours was reported, with or without chronic liver disease, respectively. Efavirenz is excreted principally in the feces, both as metabolites and unchanged drug. Approximately 14% to 34% of a radiolabeled dose of efavirenz was recovered in the urine (less than 1% as unchanged drug) and 16% to 61% of a radiolabeled dose was recovered (primarily as unchanged drug).[16]

Although the mechanism of viral resistance or reduced susceptibility to efavirenz has not been fully determined, the principal mechanism of resistance appears to be mutation of HIV RT. Like the other NNRTIs nevirapine and delavirdine, exposure to efavirenz selects for mutations that usually involve the regions of HIV RT that include amino acid positions 98 through 108 and 179 through 190, although mutations at position 225 have also been reported. Acquisition of a single mutation can result in resistance to efavirenz. HIV-1 strains with decreased susceptibility to efavirenz, nevirapine, and delavirdine have been isolated from patients receiving efavirenz in conjunction with other agents. Maintaining adequate trough concentrations of efavirenz may delay emergence of highly resistant viral variants.[17]

The potential for cross resistance between efavirenz and nucleoside reverse transcriptase inhibitors (NRTIs) is considered low because the drugs bind at different sites and have different mechanisms of action. Cross resistance between efavirenz and HIV protease inhibitors (PIs) is unlikely because of the different enzyme targets involved.[18]

## Adverse Events/Toxicity

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Efavirenz's most common adverse effects are depression, pruritis, and skin rash.

Fifty-two percent of patients treated with efavirenz reported central nervous system (CNS) or psychiatric symptoms. In 2.6% of patients, these symptoms were severe and resulted in discontinuation of efavirenz. CNS symptoms included abnormal dreams, abnormal thinking, agitation, amnesia, confusion, depersonalization, dizziness, euphoria, hallucinations, impaired concentration, insomnia, somnolence, and stupor. Symptoms usually appeared within the first or second day of treatment and generally resolved after 2 to 4 weeks.[19] [20] After 4 weeks of therapy, the prevalence of CNS symptoms of at least moderate severity ranged from 5% to 9% in patients treated with efavirenz-containing regimens, compared to 3% to 5% in patients treated with a control regimen. Adverse CNS effects may be more tolerable with bedtime dosing.[21]

## Adverse Events/Toxicity (cont.)

Depression, anxiety, and nervousness have been reported in patients taking efavirenz. Severe depression, suicidal ideation, nonfatal suicide attempts, aggressive behavior, paranoid reactions, and mania reactions have been reported in 0.4% to 1.6% of patients receiving efavirenz in controlled clinical studies. Although a causal relationship with efavirenz has not been established, there have been occasional postmarketing reports of death by suicide, delusions, or psychosis-like behavior in patients taking efavirenz. There is no evidence that patients who develop adverse CNS effects during efavirenz therapy are at greater risk of developing psychiatric symptoms.[22]

Skin rashes usually appear as mild or moderate maculopapular skin eruptions that occur within the first 2 weeks of efavirenz therapy. In controlled clinical trials, 26% of patients treated with 600 mg of efavirenz experienced new onset skin rash, compared with 18% of patients treated in control groups. In most patients, rash resolves within 1 month with continuing efavirenz therapy. Efavirenz can be reinitiated in patients interrupting therapy because of rash. Rash associated with blistering, moist desquamation, or ulceration occurred in less than 1% of patients taking efavirenz. The incidence of Grade 4 rash such as erythema multiforme or Stevens-Johnson syndrome in patients treated with efavirenz in all studies and expanded access programs was 0.1%. The discontinuation rate for rash in clinical trials was 1.7%. Efavirenz should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement, or fever.[23]

Substantial increases in liver enzymes and hepatic failure have been reported in patients receiving efavirenz, with or without coinfection with hepatitis B or C virus. It is unclear if these increases reflect drug-induced enzyme induction rather than liver toxicity. Moderate to severe gastrointestinal effects have been reported in up to 14% of adults receiving efavirenz in clinical studies. Nausea, diarrhea, vomiting, dyspepsia, abdominal pain, anorexia, constipation, and malabsorption have been reported. Although the clinical importance remains to be determined, total serum cholesterol and high-density lipoprotein (HDL) concentrations

were increased in healthy individuals receiving efavirenz. Monitoring of cholesterol and triglycerides should be considered in patients treated with efavirenz. Flushing and palpitations have been reported during postmarketing surveillance.[24]

Pancreatitis has been reported in a few patients receiving efavirenz. Asymptomatic serum amylase concentration increases to greater than 1.5 times the upper limit of normal have been reported in 10% of patients receiving efavirenz compared with 6% of patients in control groups. Lipodystrophy, moderate or severe pain, abnormal vision, arthralgia, asthenia, dyspnea, gynecomastia, myalgia, myopathy, and tinnitus have also been reported.[25]

Although the types and severity of adverse reactions related to efavirenz experienced by pediatric patients were generally similar to those of adults, children experienced a higher incidence of rash (46% of children compared to 26% of adults). The incidence of Grade 3 or 4 moderate to severe rash was also higher in children, with 5% of children developing a severe rash compared to 0.9% of adults.[26]

## Drug and Food Interactions

Efavirenz should not be taken with high fat meals, which may increase absorption of efavirenz.[27]

Metabolism of efavirenz is mediated in part by CYP3A4; drugs that induce this isoenzyme may reduce efavirenz plasma concentrations. In vitro studies have shown that efavirenz inhibits CYP2C9, CYP2C19, and CYP3A4.

Coadministration of efavirenz with drugs primarily metabolized by CYP2C9, CYP2C19, and CYP3A4 may result in altered plasma concentrations of the coadministered drug. Astemizole, cisapride, ergot alkaloids and derivatives, midazolam, or triazolam should not be used concomitantly with efavirenz.[28]

Clinically important pharmacokinetic interactions occur when efavirenz is used in conjunction with PIs. Plasma concentrations of amprenavir, indinavir, lopinavir (in fixed dose combination with ritonavir), nelfinavir, and saquinavir were decreased. However, concomitant use of ritonavir

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## **Drug and Food Interactions (cont.)**

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and efavirenz resulted in increased AUC for both drugs and a higher incidence of adverse effects. Pharmacokinetic studies evaluating concomitant use of efavirenz and the other NNRTIs have not been performed and concomitant use of these drugs is not recommended. Clinically important pharmacokinetic interactions are not expected between efavirenz and NRTIs, as these drugs have different metabolic pathways and are unlikely to compete for the same metabolic enzymes.[29]

Concurrent use of rifampin decreases efavirenz plasma concentrations; concurrent use of rifabutin does not effect efavirenz plasma concentrations but decreases rifabutin plasma concentrations. Efavirenz may decrease the plasma concentration of clarithromycin; however, coadministration of azithromycin with efavirenz did not result in any clinically significant pharmacokinetic interactions. Other macrolide antibiotics, such as erythromycin, have not been studied in combination with efavirenz.[30]

Coadministration of methadone and efavirenz decreased the C<sub>max</sub> and AUC of methadone by 45% and 52%, respectively, and resulted in manifestations of opiate withdrawal. The maintenance dosage of methadone was increased by 22% to alleviate withdrawal symptoms. Anticonvulsant levels should be monitored in patients taking efavirenz and carbamazepine, phenobarbital, or phenytoin. Administration of efavirenz in patients receiving psychoactive drugs may result in increased CNS effects.[31]

Plasma concentrations of ethinyl estradiol found in oral and other hormonal contraceptives may be increased by efavirenz; the clinical significance is unknown. The addition of a reliable method of barrier contraception is recommended for patients taking efavirenz. Concurrent use of St. John's wort (*Hypericum perforatum*) or St. John's wort-containing products with efavirenz is expected to substantially decrease efavirenz plasma concentrations, which may result in suboptimal efavirenz levels and lead to loss of virologic response or resistance to efavirenz.[32]

Plasma concentrations and clinical effects of

warfarin, a drug with a narrow therapeutic margin, may be either increased or decreased when used concurrently with efavirenz.[33]

Although efavirenz does not bind to cannabinoid receptors, false-positive urine cannabinoid test results have been reported in uninfected volunteers who received efavirenz. The false-positive results have been observed only with the CEDIA DAU Multi-Level THC assay used for screening and were not observed with other cannabinoid assays, including those used for confirmation of positive results.[34]

Based on data from an open-label randomized study and retrospective database analyses, clinicians are advised to use caution when administering tenofovir disoproxil fumarate, enteric-coated didanosine, and either efavirenz or nevirapine in the treatment of treatment-naïve HIV infected patients with high baseline viral loads.[35]

## **Contraindications**

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Efavirenz is contraindicated in patients with clinically significant hypersensitivity to any of its components. Efavirenz should not be administered concurrently with astemizole, cisapride, midazolam, triazolam, or ergot derivatives because competition for CYP3A4 could result in inhibition of metabolism of these drugs and create the potential for serious or life-threatening adverse events, such as cardiac arrhythmias, prolonged sedation, or respiratory depression. Efavirenz should not be administered concurrently with voriconazole because efavirenz significantly decreases voriconazole plasma concentrations.[36]

Risk-benefit should be considered when using efavirenz therapy for patients with impaired hepatic function and/or hepatitis B or C virus infection.[37]

## **Clinical Trials**

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For information on clinical trials that involve Efavirenz, visit the ClinicalTrials.gov web site at <http://www.clinicaltrials.gov>. In the Search box, enter: Efavirenz AND HIV Infections.

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## Dosing Information

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Mode of Delivery: Oral (capsule, tablet).[38]

Dosage Form: Capsules containing efavirenz 50, or 200 mg and film-coated tablets containing efavirenz 600 mg.[39]

The recommended dose of efavirenz for adults and children weighing more than 40 kg (88 lbs) is 600 mg once daily. Dosing recommendations for pediatric patients 3 years of age or older who weigh between 10 and 40 kg are provided in the manufacturer's prescribing information.[40]

Storage: Store at 25 C (77 F); excursions permitted between 15 C to 30 C (59 F to 86 F).[41]

## Chemistry

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CAS Name: 2H-3,1-Benzoxazin-2-one, 6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-, (4S)-[42]

CAS Number: 154598-52-4[43]

Molecular formula: C<sub>14</sub>H<sub>9</sub>ClF<sub>3</sub>N<sub>2</sub>O<sub>2</sub>[44]

C53.27%, H2.87%, Cl11.23%, F18.05%, N4.44%, O10.14%[45]

Molecular weight: 315.68[46]

Physical Description: White to slightly pink crystalline powder.[47]

Solubility: Practically insoluble in water (less than 10 mcg/ml).[48]

## Other Names

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DMP-266[49]

L 743726[50]

Stocrin[51]

EFV[52]

## Further Reading

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# Efavirenz



## **Manufacturer Information**

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### Efavirenz

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Princeton, NJ 08543-4500  
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### Sustiva

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## **For More Information**

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Contact your doctor or an AIDSinfo Health Information Specialist:

- Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET
- Via Live Help: [http://aidsinfo.nih.gov/live\\_help](http://aidsinfo.nih.gov/live_help) Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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