

Efavirenz

Brand Name: Sustiva

Drug Description

Efavirenz (EFV) is a benzoxazinone derivative nonnucleoside reverse transcriptase inhibitor (NNRTI). [1]

HIV/AIDS-Related Uses

EFV 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] EFV was approved under the FDA's accelerated review process, which allows approval based on analysis of surrogate markers or response (e.g., T cell counts, HIV RNA viral levels) rather than clinical endpoints such as disease progression or survival.[3] The safety and efficacy of EFV in children less than 3 years of age have not been established.[4]

EFV and lamivudine in combination with zidovudine, tenofovir DF, or stavudine is the preferred NNRTI-based regimen for treatment-naïve patients.[5]

EFV 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. EFV should be considered when resistance to protease inhibitors in the source person's virus is known or suspected.[6]

Pharmacology

EFV 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. EFV 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.[7]

Following oral administration of a single 100 mg to

1600 mg dose of EFV in healthy adults, peak plasma drug concentrations (C_{max}) of 0.51 to 2.9 mcg/ml were attained within 5 hours. Increases in C_{max} and area under the plasma concentration-time curve (AUC) were dose proportional for 200, 400, and 600 mg EFV doses; the increases were less than proportional for a 1600 mg EFV dose, suggesting reduced absorption at higher doses. Time 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 EFV dose in individuals with chronic liver disease or healthy individuals, C_{max} averaged 1.2 or 1.8 mcg/ml, respectively, and AUC averaged 94.4 or 96.3 mcg·hr/ml.[8]

Normal meals had no significant effect on the bioavailability of 100 mg of EFV administered twice a day for 10 days. The relative bioavailability of a single 1200 mg dose of EFV in uninfected volunteers was increased by 50% following a high fat meal.[9]

Distribution of EFV into body tissues and fluids has not been fully characterized. In animal models, EFV's volume of distribution following IV administration suggests extensive tissue distribution. In HIV infected patients who received 200 mg to 600 mg of EFV 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 EFV in plasma. EFV is highly bound (approximately 99.5% to 99.75%) to human plasma proteins, principally albumin.[10]

EFV is in FDA Pregnancy Category C; no adequate and well-controlled studies have been performed in pregnant women. In animal studies, EFV crossed the placenta and resulted in fetal blood concentrations similar to maternal blood concentrations. Pregnancy should be avoided in women receiving EFV due to teratogenicity observed in nonhuman primate studies at plasma concentrations similar to those used in humans. Two methods of birth control (a barrier method in combination with a nonbarrier method such as an

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Pharmacology (cont.)

oral or other hormonal contraceptive) should be used to avoid pregnancy. Before initiating therapy with EFV, women of childbearing potential should undergo pregnancy testing. It is recommended that EFV not be given to pregnant women except in a situation in which there are no therapeutic alternatives. An Antiretroviral Pregnancy Registry has been established to monitor the outcomes of pregnant women exposed to EFV. Physicians may register patients by calling (800) 258-4263. It is not known whether EFV is distributed into breast milk in humans; however, EFV is distributed into the milk of laboratory animals. Breastfeeding is not recommended during EFV therapy.[11]

EFV is metabolized primarily by the hepatic cytochrome P450 isoenzymes CYP3A4 and CYP2B6 into hydroxylated, inactive metabolites. These metabolites undergo subsequent glucuronidation. EFV is an inducer of its own metabolism. Ten days of therapy with 200 mg to 400 mg of EFV 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 with the single-dose half-life of 52 to 76 hours.[12]

Terminal elimination half-life is prolonged in patients with chronic liver disease.

EFV is excreted principally in the feces, both as metabolites and unchanged drug. Approximately 14% to 34% of a radiolabeled dose of EFV 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).[13]

Although the mechanism of viral resistance or reduced susceptibility to EFV has not been fully determined, the principal mechanism of resistance appears to be mutation of HIV RT. Like other NNRTIs (nevirapine, delavirdine), exposure to EFV 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 EFV.

HIV-1 strains with decreased susceptibility to EFV,

nevirapine, and delavirdine have been isolated from patients receiving EFV in conjunction with other agents. Maintaining adequate trough concentrations of EFV may delay emergence of highly resistant viral variants.

The potential for cross-resistance between EFV and nucleoside reverse transcriptase inhibitors is considered low because the drugs bind at different sites and have different mechanisms of action. Cross-resistance between EFV and HIV protease inhibitors is unlikely because of the different enzyme targets involved.[14]

Adverse Events/Toxicity

EFV's principal adverse effects are nervous system effects, psychiatric symptoms, and dermatologic effects.[15]

Fifty-two percent of patients treated with EFV reported CNS or psychiatric symptoms. In 2.6% of patients, these symptoms were severe and resulted in discontinuation of EFV. CNS symptoms include abnormal dreams, abnormal thinking, agitation, amnesia, confusion, depersonalization, dizziness, euphoria, hallucinations, impaired concentration, insomnia, somnolence, and stupor. Symptoms usually appear within the first or second day of treatment and generally resolve after 2 to 4 weeks. After 4 weeks of therapy, the prevalence of CNS symptoms of at least moderate severity ranged from 5% to 9% in patients treated with EFV-containing regimens, compared to 3% to 5% in patients treated with a control regimen. Adverse CNS effects may be more tolerable with bedtime dosing.[16] [17]

Depression, anxiety, and nervousness have been reported in patients taking EFV. 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 EFV in controlled clinical studies. Although a causal relationship with EFV has not been established, there have been occasional postmarketing reports of death by suicide, delusions, or psychosis-like behavior in patients taking EFV. There is no evidence that patients who develop adverse CNS effects during EFV therapy are at greater risk of developing psychiatric symptoms.[18]

Adverse Events/Toxicity (cont.)

Skin rashes usually appear as mild or moderate maculopapular skin eruptions that occur within the first 2 weeks of EFV therapy. In controlled clinical trials, 26% of patients treated with 600 mg of EFV experienced new onset skin rash, compared with 18% of patients treated in control groups. In most patients, rash resolves within 1 month with continuing EFV therapy. EFV 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 EFV. The incidence of Grade 4 rash (e.g., erythema multiforme, Stevens-Johnson Syndrome) in patients treated with EFV in all studies and expanded access programs was 0.1%. The discontinuation rate for rash in clinical trials was 1.7%. EFV should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement, or fever.[19]

Substantial increases in liver enzymes and hepatic failure have been reported in patients receiving EFV, with or without coinfection with hepatitis B and/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 EFV in clinical studies. Nausea, diarrhea, vomiting, dyspepsia, abdominal pain, anorexia, constipation, and malabsorption have been reported.

While the clinical importance remains to be determined, total serum cholesterol and HDL concentrations were increased in healthy individuals receiving EFV. Monitoring of cholesterol and triglycerides should be considered in patients treated with EFV.[20]

Pancreatitis has been reported in a few patients receiving EFV. Asymptomatic serum amylase concentration increases to greater than 1.5 times the upper limit of normal have been reported in 10% of patients receiving EFV 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.[21]

While the types and severity of adverse reactions experienced by pediatric patients were generally similar to those of adults, children experienced a higher incidence of rash (40% of children compared with 28% of adults). The incidence of severe rash (Grade 3 or 4) was also higher in children, with 7% of children developing a severe rash compared with 0.7% of adults. The median time to onset of rash in children was 8 days.[22]

Drug and Food Interactions

EFV may be taken with or without meals; however, it should not be taken with meals with a high fat content, which may increase absorption of EFV.[23]

Metabolism of EFV is mediated in part by CYP isoenzyme CYP3A4; drugs that induce this isoenzyme may reduce EFV plasma concentrations. In vitro studies have shown that EFV inhibits CYP isoenzymes CYP2C9, CYP2C19, and CYP3A4. Coadministration of EFV with drugs primarily metabolized by 2C9, 2C19, and 3A4 isoenzymes 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 EFV.[24]

Clinically important pharmacokinetic interactions occur when EFV is used in conjunction with protease inhibitors. Plasma concentrations of amprenavir, indinavir, lopinavir (in fixed dose combination with ritonavir), nelfinavir, and saquinavir were decreased. However, concomitant use of ritonavir and EFV resulted in increased AUC for both drugs and a higher incidence of adverse effects. Pharmacokinetic studies evaluating concomitant use of EFV 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 EFV and nucleoside reverse transcriptase inhibitors, as these drugs have different metabolic pathways and are unlikely to compete for the same metabolic enzymes.

Concurrent use of rifampin decreases EFV plasma concentrations; concurrent use of rifabutin does not

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Drug and Food Interactions (cont.)

effect EFV plasma concentrations but decreases rifabutin plasma concentrations.

Coadministration of voriconazole and efavirenz is contraindicated, because efavirenz significantly decreases voriconazole plasma concentrations, whereas voriconazole also significantly increases efavirenz plasma concentrations.[25] Steady state efavirenz decreased the steady state C_{max} and AUC of voriconazole by an average of 61% and 77%, respectively, in healthy subjects.

Voriconazole at steady state increased the steady state C_{max} and AUC of efavirenz by an average of 38% and 44%, respectively, in health subjects.[26]

EFV may decrease the plasma concentration of clarithromycin; however, coadministration of azithromycin with EFV did not result in any clinically significant pharmacokinetic interactions. Other macrolide antibiotics, such as erythromycin, have not been studied in combination with EFV.[27]

Administration of methadone and EFV decreased the C_{max} and AUC of methadone by 42% 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 EFV and carbamazepine, phenobarbital, or phenytoin. Administration of EFV in patients receiving psychoactive drugs may result in increased CNS effects.

Plasma concentrations of ethinyl estradiol (as in oral and other hormonal contraceptives) may be increased by EFV; the clinical significance is unknown. The addition of a reliable method of barrier contraception is recommended for patients taking EFV.[28]

Plasma concentrations and clinical effects of warfarin, a drug with a narrow therapeutic margin, may be either increased or decreased when used concurrently with EFV.[29]

Concurrent use of St. John's wort (*Hypericum perforatum*) or St. John's wort-containing products

with EFV is expected to substantially decrease EFV plasma concentrations, which may result in suboptimal EFV levels and lead to loss of virologic response and/or resistance to EFV.[30]

Although EFV does not bind to cannabinoid receptors, false-positive urine cannabinoid test results have been reported in uninfected volunteers who received EFV. 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.[31]

Contraindications

EFV is contraindicated in patients with clinically significant hypersensitivity to any of its components. EFV 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 and/or life-threatening adverse events (e.g., cardiac arrhythmias, prolonged sedation, or respiratory depression).[32]

Risk-benefit should be considered when using EFV therapy for patients with impaired hepatic function and/or hepatitis B or C virus infection.[33]

Clinical Trials

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.

Dosing Information

Mode of Delivery: Oral.[34]

Dosage Form: Capsules containing 50, 100, or 200 mg of efavirenz and film-coated tablets containing 600 mg of efavirenz.

The recommended dose of EFV for adults and children weighing more than 40 kg (88 lbs) is 600 mg once daily. Dosing recommendations for

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Dosing Information (cont.)

pediatric patients 3 years of age or older who weigh between 10 and 40 kg are provided in the Sustiva Prescribing Information.[35]

Storage: Store at 25 C (77 F); excursions permitted to 15 to 30 C (59 to 86 F).[36]

Chemistry

CAS Name: 2H-3,1-Benzoxazin-2-one, 6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-, (4S)-[37]

CAS Number: 154598-52-4[38]

Molecular formula: C₁₄H₉ClF₃N₂O₂[39]

C53.27%, H2.87%, Cl11.23%, F18.05%, N4.44%, O10.14%[40]

Molecular weight: 315.67[41]

Physical Description: White to slightly pink crystalline powder.[42]

Solubility: Practically insoluble in water, less than 10 mcg/ml.[43]

Other Names

(S)-6-Chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one[44]

DMP-266[45]

L 743726[46]

Stocrin[47]

(4S)-6-Chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one[48]

EFV[49]

Further Reading

Gallego L, Barreiro P, Rio Rd R, Gonzalez De

Requena D, Rodriguez-Albarino A, Gonzalez-Lahoz J, Soriano V. Analyzing Sleep Abnormalities in HIV-Infected Patients Treated with Efavirenz. *Clin Infect Dis.* 2004 Feb 1; 38(3): 430-2.

Jordan WC, Jefferson R, Yemofio F, Tolbert L, Conlon V, Carroll H, Green DC, Green A, Green R. Nevirapine plus efavirenz plus didanosine: a simple, safe, and effective once-daily regimen for patients with HIV infection. *J Natl Med Assoc.* 2003 Dec; 95(12): 1152-7.

Ena J, Amador C, Benito C, Fenoll V, Pasquau F. Risk and determinants of developing severe liver toxicity during therapy with nevirapine and efavirenz-containing regimens in HIV-infected patients. *Int J STD AIDS.* 2003 Nov; 14(11): 776-81.

Fowler MG, Moorman A, Tong TC, Holmberg S, Greenberg AE. Does prior short-course nevirapine reduce the effectiveness of subsequent combination treatment with efavirenz? *J Acquir Immune Defic Syndr.* 2003 Nov 1; 34(3): 348-50.

Manufacturer Information

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For More Information

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 Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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References

1. AHFS Drug Information - 2003; p. 657.
2. FDA - Approval Letter. Available at: <http://www.fda.gov/cder/foi/applletter/1998/20972ltr.pdf>. Accessed January 20, 2004.
3. AHFS Drug Information - 2003; p. 649.
4. USP DI - 2003; p. 1187.
5. Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents - MMWR 2002;51 (No.RR-7) Updated as a Living Document on November 10, 2003 p.15. Available at http://aidsinfo.nih.gov/guidelines/adult/AA_111003.pdf.
6. U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis - MMWR 2001;50 (No. RR-11); p. 12. Available at: http://www.aidsinfo.nih.gov/guidelines/health-care/HC_062901.pdf.
7. AHFS Drug Information - 2003; p. 655.
8. AHFS Drug Information - 2003; p. 656.
9. USP DI - 2003; p. 1184.
10. AHFS Drug Information - 2003; p. 656.
11. USP DI - 2003; p. 1184.
12. USP DI - 2003; p. 1184.
13. AHFS Drug Information - 2003; p. 656.
14. AHFS Drug Information - 2003; p. 656.
15. AHFS Drug Information - 2003; p. 651.
16. AHFS Drug Information - 2003; p. 651.
17. USP DI - 2003; p. 1185.
18. AHFS Drug Information - 2003; p. 651.
19. AHFS Drug Information - 2003; p. 651.
20. AHFS Drug Information - 2003; p. 652.
21. AHFS Drug Information - 2003; p. 652.
22. USP DI - 2003; pp. 1184-85.
23. USP DI - 2003; p. 1184.
24. AHFS Drug Information - 2003; p. 653.
25. FDA - Vfenid Prescribing Information, p. 20. Available at: http://www.fda.gov/cder/foi/label/2004/21266slr005,006,21267slr005,006,21630slr001_vfenid_lbl.pdf. Accessed 5/24/04.
26. FDA - Vfenid Prescribing Information, p. 11. Available at: http://www.fda.gov/cder/foi/label/2004/21266slr005,006,21267slr005,006,21630slr001_vfenid_lbl.pdf. Accessed 5/24/04.
27. USP DI - 2003; p. 1185.
28. AHFS Drug Information - 2003; pp. 654-65.
29. USP DI - 2003; p. 1185.

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30. AHFS Drug Information - 2003; p. 655.
31. USP DI - 2003; p. 1185.
32. BMS Virology - Sustiva Prescribing Information. June 2003. Available at: www.sustiva.com. Accessed January 19, 2004.
33. USP DI - 2003; pp. 1184-5.
34. USP DI - 2003; p. 1186.
35. BMS Virology - Sustiva Prescribing Information. June 2003. Available at: www.sustiva.com. Accessed January 19, 2004.
36. USP DI - 2003; p. 1186.
37. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/detail_frame.html?DetailIndex=1&DetailCount=1. Accessed January 19, 2004.
38. USP Dictionary of USAN & Intern. Drug Names - 2003; p. 304.
39. USP Dictionary of USAN & Intern. Drug Names - 2003; p. 304.
40. Merck Index - 13th Edition; pp. 621-22.
41. USP Dictionary of USAN & Intern. Drug Names - 2003; p. 304.
42. AHFS Drug Information - 2003; p. 657.
43. BMS Virology - Sustiva Prescribing Information. June 2003. Available at: www.sustiva.com. Accessed January 19, 2004.
44. USP Dictionary of USAN & Intern. Drug Names - 2003; p. 304.
45. Merck Index - 13th Edition; p. 621-22.
46. Merck Index - 13th Edition; p. 621-22.
47. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/detail_frame.html?DetailIndex=1&DetailCount=1. Accessed January 19, 2004.
48. Merck Index - 13th Edition; p. 621-22.
49. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/detail_frame.html?DetailIndex=1&DetailCount=1. Accessed January 19, 2004.