Efavirenz / Emtricitabine / Tenofovir disoproxil fumarate

Brand Name: Atripla
Drug Class: Combination Drugs

Drug Description

Atripla is a fixed-dose combination tablet containing three antiretroviral medications. One tablet of Atripla is equivalent to one tablet of efavirenz 600 mg, a non-nucleoside reverse transcriptase inhibitor (NNRTI), and one tablet of Truvada. Truvada is a fixed-dose combination tablet of two nucleoside reverse transcriptase inhibitors (NRTIs), emtricitabine 200 mg and tenofovir disoproxil fumarate (tenofovir DF) 300 mg. [1] These three FDA-approved antiretroviral medications have been administered as separate pills in combination for the treatment of HIV infection before the development of Atripla. [2]

HIV/AIDS-Related Uses

Atripla (efavirenz, emtricitabine, and tenofovir DF) was approved by the FDA on July 12, 2006, for the treatment of HIV-1 infection in adults.[3] Atripla is indicated as a complete regimen or in combination with other antiretroviral medications. Clinical studies support use of Atripla in antiretroviral-naive patients.[4] Atripla is not recommended for use in the pediatric population.[5]

Pharmacology

One Atripla tablet is bioequivalent to one efavirenz tablet (600 mg), one emtricitabine capsule (200 mg), and one tenofovir DF tablet (300 mg) after single-dose administration to fasting healthy volunteers.[6] In combination studies evaluating the antiviral activity of emtricitabine and efavirenz together, efavirenz and tenofovir together, and emtricitabine and tenofovir together, additive to synergistic antiviral effects were observed.[7]

Efavirenz is an NNRTI. Efavirenz activity is mediated predominantly by noncompetitive inhibition of HIV-1 reverse transcriptase (RT). Emtricitabine, a synthetic nucleoside analog of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate, which inhibits the activity of the HIV-1 RT by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into nascent viral DNA, resulting in chain termination. Tenofovir DF is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir DF requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 RT by competing with the natural substrate deoxyadenosine 5'-triphosphate and terminates the chain after incorporation into DNA.[8] (For more information, see individual drug fact sheets for efavirenz, emtricitabine, and tenofovir DF.)

In HIV infected patients, time-to-peak plasma concentrations (Cmax) of efavirenz were approximately 3 to 5 hours, and steady-state plasma concentrations were reached in 6 to 10 days. In 35 patients receiving efavirenz 600 mg once daily, the mean Cmax was 12.9 g/ml, and the mean area under the concentration-time curve (AUC) was 184 g(hr)/ml. Efavirenz is nearly 100% bound to plasma proteins, predominantly albumin. In vitro studies suggest cytochrome P450 (CYP) 3A4 and CYP2B6 are the major isozymes responsible for efavirenz metabolism. Efavirenz has been shown to induce CYP enzymes, resulting in induction of its own metabolism. Efavirenz has a terminal half-life of 52 to 76 hours after single doses and of 40 to 55 hours after multiple doses. Between 14% and 34% of efavirenz, mostly as metabolites, is eliminated renally; 16% to 61%, mostly as parent drug, is recovered in the feces.[9]

Following oral administration, emtricitabine is rapidly absorbed, with the Cmax occurring at 1 to 2 hours post-dose. Following multiple-dose, oral administration of emtricitabine to 20 HIV infected patients, the steady-state mean Cmax was 1.8 g/ml, and the mean AUC was 10.0 g hr/ml. The mean absolute bioavailability of emtricitabine was 93%. In vitro binding of emtricitabine to human plasma proteins is less than 4% and is independent of concentration over the range of 0.02 to 200 g/ml. Emtricitabine is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose, the half-life is approximately 10 hours. Approximately 86% of emtricitabine is recovered in the urine, and 13% is recovered as metabolites.[10]

Efavirenz / Emtricitabine / Tenofovir disoproxil fumarate

Pharmacology (cont.)

Following oral administration of a single, 300-mg dose of tenofovir DF to fasting patients, the mean Cmax (achieved in approximately 1 hour) was 296 ng/ml, and the mean AUC was 2,287 ng(h)/ml. The oral bioavailability of tenofovir from tenofovir DF in fasting patients is approximately 25%. In vitro binding of tenofovir to human plasma proteins is less than 0.7% and is independent of concentration over the range of 0.01 to 25 g/ml. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose, the terminal elimination half-life is approximately 17 hours. Approximately 79% to 80% of an IV dose is recovered unchanged in the urine.[11]

Atripla is in FDA Pregnancy Category D. There are no adequate and well-controlled studies of Atripla in pregnant women. Pregnancy should be avoided in women receiving Atripla. Barrier contraception should always be used in combination with other methods of contraception. Atripla 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. To monitor fetal outcomes of pregnant women, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients who become pregnant online at http://www.APRegistry.com or by calling 1-800-258-4263.[12]

As of July 2006, the Antiretroviral Pregnancy Registry has received prospective reports of 322 pregnancies exposed to efavirenz-containing regimens, nearly all of which (316) were first-trimester exposures. Birth defects occurred in 6 of 255 live births after first-trimester exposure and in 1 of 17 live births after second- or third-trimester exposure. None of these prospectively reported defects were neural tube defects. However, there have been four retrospective reports of findings consistent with neural tube defects, including meningomyelocele. All mothers were exposed to efavirenz-containing regimens in the first trimester. Although a causal relationship of these events to the use of efavirenz has not been established, similar defects have been observed in preclinical studies of efavirenz.[13]

HIV-1 isolates with reduced susceptibility to the combination of emtricitabine and tenofovir have been selected in cell culture and in clinical studies. Genotypic analysis of these isolates identified the M184V/I and K65R amino acid substitutions in the viral reverse transcriptase.[14] The most frequently observed amino acid substitution in clinical studies with efavirenz is K103N. Reduced susceptibility to emtricitabine is associated with the M184V/I mutation. Reduced susceptibility to tenofovir selected in cell culture was expressed as a K65R mutation.[15]

In a clinical study of treatment-naive patients receiving efavirenz in combination with emtricitabine and tenofovir DF or with zidovudine/lamivudine, genotypic resistance to efavirenz, predominantly the K103N substitution, was the most common form of resistance that developed. Resistance to efavirenz occurred in 9/12 (75%) patients in the emtricitabine/tenofovir DF group and in 16/22 (73%) patients in the zidovudine/lamivudine group.[16]

Adverse Events/Toxicity

Adverse effects commonly associated with efavirenz use include impaired concentration, anorexia, abdominal pain, anxiety, and pruritus. Pancreatitis has been reported, although a causal relationship with efavirenz has not been established.[17]

Adverse effects that occurred in at least 5% of patients receiving emtricitabine and tenofovir DF include anxiety, arthralgia, increased cough, dyspepsia, fever, myalgia, abdominal pain, peripheral neuropathy, rash, pruritus, urticaria, and paresthesia. Skin discoloration has been reported with higher frequency among emtricitabine-treated patients. The hyperpigmentation of the palms and soles was generally mild and asymptomatic.[18] (For more information on adverse effects of each drug, please see individual drug fact sheets for efavirenz, emtricitabine, and tenofovir DF.)

Study 934 reported adverse events associated with the combination of efavirenz and Truvada (emtricitabine and tenofovir DF). The most common adverse reactions were diarrhea, nausea, fatigue, dizziness, headache, and rash. In HIV

Adverse Events/Toxicity (cont.)

infected patients taking efavirenz and Truvada, elevated fasting cholesterol and serum amylase were noted in 15% and 7% of patients, respectively.[19]

Drug and Food Interactions

Atripla should be taken on an empty stomach.[20] However, Atripla has not been evaluated in the presence of food. Administration of efavirenz with a high-fat meal increased the mean Cmax significantly compared with the fasted state.[21]

Saquinavir should not be the only protease inhibitor administered with Atripla. Atazanavir and lopinavir/ritonavir may increase tenofovir concentrations and tenofovir-related adverse effects, and atazanavir concentrations may be reduced with concomitant Atripla administration. In addition, patients receiving concomitant Atripla and didanosine should be monitored for didanosine-related adverse effects.[22]

Contraindications

Atripla is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the product.[23]

Tenofovir DF and efavirenz have not been studied in patients younger than 3 years of age or weighing less than 13 kg (28.7 lbs). Atripla is not recommended for pediatric administration.[24]

Atripla should not be administered concurrently with midazolam, triazolam, or ergot derivatives, because competition for CYP3A4 liver enzymes by efavirenz could result in inhibition of metabolism of these drugs and could create the potential for serious adverse events, including cardiac arrhythmias and respiratory depression. Atripla should not be coadministered with voriconazole, because efavirenz significantly decreases voriconazole plasma concentrations.[25]

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination with other antiretrovirals. The safety of Atripla has not been established in patients coinfected with HIV and hepatitis B virus (HBV). Severe acute exacerbations of HBV have been reported in patients who have discontinued emtricitabine or tenofovir DF. Hepatic function should be monitored closely for at least several months in patients who discontinue Atripla and are coinfected with HIV and HBV. If appropriate, initiation of HBV therapy may be warranted.[26] Atripla is not indicated for use in patients coinfected with HIV and chronic HBV.[27]

Because of the nature of the fixed-dose combination tablet, Atripla should not be used in combination with the individual component medications efavirenz, emtricitabine, and tenofovir DF. In addition, because of similarities between emtricitabine and lamivudine, Atripla should not be coadministered with drugs containing lamivudine, including the brand medications Combivir, Epivir, Epzicom, or Trizivir.[28]

Clinical Trials

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

Dosing Information

Mode of Delivery: Oral.[29]

Dosage Form: Film-coated tablet containing efavirenz 600 mg, emtricitabine 200 mg, and tenofovir DF 300 mg.[30]

The recommended adult dose of Atripla is one tablet once daily on an empty stomach, alone or in combination with other antiretroviral medications.[31]

Storage: Store tablets in a tightly closed container at 25 C (77 F), with excursions permitted at 15 C to 30 C (59 F to 86 F).[32]

Efavirenz / Emtricitabine / Tenofovir disoproxil fumarate

Chemistry

CAS Name: Efavirenz: 2H-3,1-Benzoxazin-2-one, 6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-, (4S)-[33]

Emtricitabine: (2R-cis)-4-Amino-5-fluoro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl] -2(1H)-pyrimidinone[34]

Tenofovir DF: Bis(hydroxymethyl) [[(R)-2(6-Amino- 9H-purin-9-yl)-1-methylethoxy] methyl]phosphonate,bis(isopropyl carbonate) (ester), fumarate (1:1)[35]

CAS Number: Efavirenz: 154598-52-4[36]

Emtricitabine: 143491-57-0[37]

Tenofovir DF: 147127-20-6[38]

Molecular formula: Efavirenz: C14-H9-Cl-F3-N-O2; Emtricitabine: C8-H10-F-N3-O3-S; Tenofovir DF: C19-H30-N5-O10-P.C4-H4-O4[39]

Efavirenz: C53.27%, H2.87%, Cl11.23%, F18.05%, N4.44%, O10.14%; Emtricitabine: C38.86%, H4.08%, F7.68%, N17.00%, O19.41%, S12.97%; Tenofovir DF: C43.47%, H5.39%, N11.02%, O35.25%, P4.87%[40]

Molecular weight: Efavirenz: 315.68; Emtricitabine: 247.25; Tenofovir DF: 635.51[41]

Melting point: Efavirenz: 139 C to 141 C; Emtricitabine: 136 C to 140 C (276.8 F to 284 F) as solid white from ether and methanol.[42]

Physical Description: Efavirenz: White to slightly pink crystalline powder.[43]

Emtricitabine: White to off-white crystalline powder.[44]

Tenofovir DF: White to off-white crystalline powder.[45]

Solubility: Efavirenz: Practically insoluble in water (less than 10 mcg/ml); Emtricitabine: Soluble in 25 C at 112 mg/ml; Tenofovir DF: Soluble in 25 C water at 13.4 mg/ml.[46]

Further Reading

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Manufacturer Information

Efavirenz / Emtricitabine / Tenofovir disoproxil fumarate
Bristol - Myers Squibb Co
PO Box 4500
Princeton, NJ 08543-4500
(800) 321-1335

Efavirenz / Emtricitabine / Tenofovir disoproxil fumarate
Gilead Sciences Inc
333 Lakeside Dr
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• 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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