PRESCRIBING INFORMATION

Stavudine 40 mg and Lamivudine 150 mg Tablets Co-Packaged with Efavirenz 600 mg Tablets

R_X only

WARNINGS

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING STAVUDINE AND LAMIVUDINE AND OTHER ANTIRETROVIRALS (SEE **WARNIGS AND PRECAUTIONS**).

FATAL LACTIC ACIDOSIS HAS BEEN REPORTED IN PREGNANT WOMEN WHO RECEIVED THE COMBINATION OF STAVUDINE AND DIDANOSINE WITH OTHER ANTIRETROVIRAL AGENTS. THE COMBINATION OF STAVUDINE AND DIDANOSINE SHOULD BE USED WITH CAUTION DURING PREGNANCY AND IS RECOMMENDED ONLY IF THE POTENTIAL BENEFIT CLEARLY OUTWEIGHS THE POTENTIAL RISK (SEE **WARNINGS AND PRECAUTIONS: PREGNANCY**).

FATAL AND NONFATAL PANCREATITIS HAVE OCCURED DURING THERAPY WHEN STAVUDINE WAS PART OF A COMBINATION REGIMEN THAT INCLUDED DIDANOSINE, WITH OR WITHOUT HYDROXYUREA, IN BOTH TREATMENT–NAIVE AND TREATMENT EXPERIENCED PATIENTS, REGARDLESS OF DEGREE OF IMMUNOSUPPRESSION (SEE **WARNINGS**).

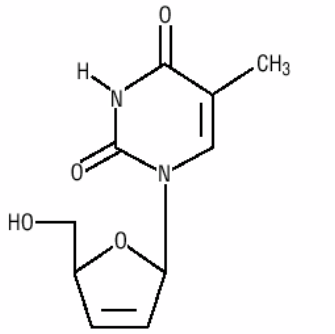
SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO ARE CO-INFECTED WITH HEPATITIS B VIRUS (HBV) AND HIV AND HAVE DISCONTINUED LAMIVUDINE. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE STAVUDINE AND LAMIVUDINE TABLETS AND ARE CO-INFECTED WITH HIV AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (**SEE WARNINGS**).

DESCRIPTION

Stavudine and lamivudine are synthetic nucleoside analogues and efavirenz is a non-nucleoside reverse transcriptase inhibitor that have activity against human immunodeficiency virus. Stavudine 40 mg and Lamivudine 150 mg Tablets co-packaged with Efavirenz 600 mg Tablets are for oral administration. Each Stavudine 40 mg/lamivudine 150 mg Tablet contains the active ingredients 40 mg of stavudine and 150 mg of lamivudine and the inactive ingredients microcrystalline cellulose, colloidal anhydrous silica, croscarmellose sodium, ferric oxide red, povidone, magnesium stearate and purified water. Efavirenz 600mg Tablet contains active ingredient efavirenz 600mg and the inactive ingredients croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The film coating contains Opadry® Brown. Opadry® Brown contains HPMC 2910/Hypromellose, titanium dioxide, macrogol/PEG 400, iron oxide yellow, iron oxide red and iron oxide black.

Stavudine

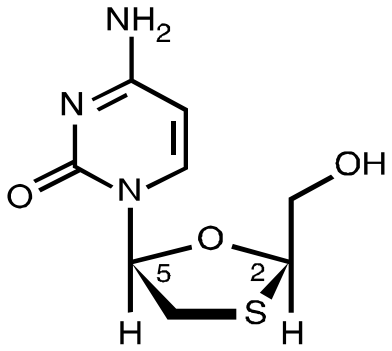
The chemical name for stavudine is 2',3'-didehydro-3'-deoxythymidine. Stavudine has the following structural formula:



Stavudine is a white to off-white crystalline solid with the molecular formula $C_{10}H_{12}N_2O_4$ and a molecular weight of 224.22. The solubility of stavudine at 23° C is approximately 83 mg/mL in water and 30 mg/mL in propylene glycol. The n-octanol/water partition coefficient of stavudine at 23° C is 0.144.

Lamivudine

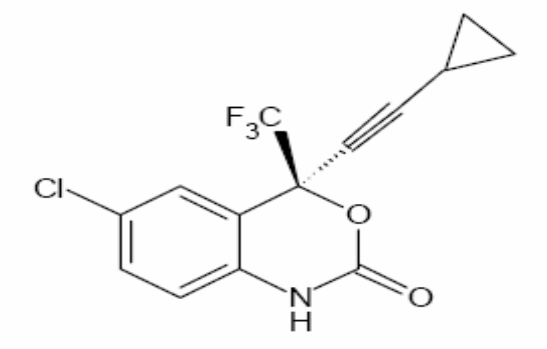
The chemical name of lamivudine is (-)-1-[(2R,5S)-2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2′,3′-dideoxy, 3′- thiacytidine.. It has the following structural formula:



Lamivudine is a white to off-white crystalline solid with the molecular formula $C_8H_{11}N_3O_3S$ and a molecular weight of 229.26. It has solubility of approximately 70 mg/mL in water at 20^oC.

Efavirenz

Efavirenz is a white to slightly pink crystalline powder with the molecular weight of 315.68 and the empirical formula $C_{14}H_9ClF_3NO_2$. The chemical name of efavirenz is (S)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one. Efavirenz has the following structure:



MICROBIOLOGY

Mechanism of Action

Stavudine: Stavudine, a nucleoside analogue of thymidine, is phosphorylated by cellular kinases to the active metabolite stavudine triphosphate. Stavudine triphosphate inhibits the activity of

human immunodeficiency virus type 1 (HIV-1) reverse transcriptase (RT) by competing with the natural substrate thymidine triphosphate (K_i = 0.0083 to 0.032 μM), and by causing DNA chain

termination following its incorporation into viral DNA. Stavudine triphosphate inhibits cellular DNA polymerases β and γ and markedly reduces the synthesis of mitochondrial DNA.

Lamivudine: Lamivudine is a synthetic nucleoside analogue. Intracellularly, lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is the inhibition of HIV-1 reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleoside analogue into viral DNA. 3TC-TP is a weak inhibitor of mammalian DNA polymerases α, β and γ.

Efavirenz: Efavirenz (EFV) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. EFV activity is mediated predominantly by noncompetitive inhibition of HIV-1 RT. Human immunodeficiency virus type 2 (HIV-2) RT and human cellular DNA polymerases α, β, γ, and δ are not inhibited by EFV.

Antiviral Activity

Stavudine: The antiviral activity of stavudine was measured in peripheral blood mononuclear cells, monocytic cells, and lymphoblastoid cell lines. The concentration of drug necessary to inhibit HIV-1 replication by 50% (EC_{50}) ranged from 0.009 to 4 μM against laboratory and clinical isolates of HIV-1. In cell culture, stavudine exhibited additive to antagonistic activity in combination with zidovudine. Stavudine in combination with either abacavir, didanosine, tenofovir, or zalcitabine exhibited additive to synergistic anti-HIV-1 activity. Ribavirin, at the 9-45 μM concentrations tested, reduced the anti-HIV-1 activity of stavudine by 2.5- to 5-fold.

Lamivudine: The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes) using standard susceptibility assays. EC_{50} values (50% effective concentrations) were in the range of 0.003 to 15 μM (1 μM = 0.23 mcg/mL). The EC_{50} values of lamivudine against different HIV-1 clades (A-G) ranged from 0.001 to 0.120 μM, and against HIV-2 isolates from 0.003 to 0.120 μM. Ribavirin (50 μM) decreased the anti-HIV-1 activity of lamivudine by 3.5 fold. In HIV–1-

infected MT-4 cells, lamivudine in combination with zidovudine at various ratios exhibited synergistic antiretroviral activity.

Efavirenz: The concentration of EFV inhibiting in cell culture replication of wild-type laboratory adapted strains and clinical isolates by 90-95% (EC_{90-95}) ranged from 1.7 to 25 nM in lymphoblast cell lines, peripheral blood mononuclear cells (PBMCs), and macrophage/monocyte cultures. EFV demonstrated antiviral activity against most non-clade B isolates (subtypes A, AE, AG, C, D, F, G, J, N), but had reduced antiviral activity against group O viruses. EFV demonstrated additive antiviral activity without cytotoxicity against HIV-1 in cell culture when combined with the NNRTIs delavirdine (DLV) and nevirapine (NVP), NRTIs (abacavir, didanosine, emtricitabine, lamivudine [LAM], stavudine, tenofovir, zalcitabine, zidovudine [ZDV]), PIs (amprenavir, indinavir [IDV], lopinavir, nelfinavir, ritonavir, saquinavir), and the fusion inhibitor enfuvirtide. EFV demonstrated additive to antagonistic antiviral activity in cell culture with atazanavir. EFV was not antagonistic with adefovir, used for the treatment of hepatitis B virus infection, or ribavirin, used in combination with interferon for the treatment of hepatitis C virus infection.

Resistance

Stavudine: HIV-1 isolates with reduced susceptibility to stavudine have been selected in cell culture (strain-specific) and were also obtained from patients treated with stavudine. Phenotypic analysis of HIV-1 isolates from 61 patients receiving prolonged (6 to 29 months) stavudine monotherapy showed that post-therapy isolates from four patients exhibited EC_{50} values more than 4-fold (range 7- to 16-fold) higher than the average pretreatment susceptibility of baseline isolates. Of these, HIV-1 isolates from one patient contained the zidovudine-resistance-associated substitutions T215Y and K219E, and isolates from another patient contained the multiple-nucleoside-resistance-associated substitution Q151M. Mutations in the RT gene of HIV-1 isolates from the other two patients were not detected.

Lamivudine: Lamivudine-resistant variants of HIV-1 have been selected in cell culture. Genotypic analysis showed that the resistance was due to a specific amino acid substitution in

the HIV-1 reverse transcriptase at codon 184 changing the methionine residue to either isoleucine or valine.

Clinical Studies

HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from patients. Susceptibility of clinical isolates to lamivudine and zidovudine was monitored in controlled clinical trials. In patients receiving lamivudine monotherapy or combination therapy with lamivudine plus zidovudine, HIV-1 isolates from most patients became phenotypically and genotypically resistant to lamivudine within 12 weeks. In some patients harboring zidovudine-resistant virus at baseline, phenotypic sensitivity to zidovudine was restored by 12 weeks of treatment with lamivudine and zidovudine. Combination therapy with lamivudine plus zidovudine delayed the emergence of mutations conferring resistance to zidovudine.

Amino acid substitutions in the HBV polymerase YMDD motif have been associated with reduced susceptibility of HBV to lamivudine in cell culture. In studies of non-HIV-infected patients with chronic hepatitis B virus infection, isolates with YMDD mutations were detected in some patients who received lamivudine daily for 6 months or more, and were associated with evidence of diminished treatment response; similar HBV mutants have been reported in HIV-infected patients who received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus (see **PRECAUTIONS** and EPIVIR-HBV® package insert).

Efavirenz: HIV-1 isolates with reduced susceptibility to EFV (>380-fold increase in EC_{90} value) emerged rapidly under in cell culture selection. Genotypic characterization of these viruses identified mutations resulting in single amino acid substitutions L100I or V179D, double substitutions L100I/V108I, and triple substitutions L100I/V179D/ Y181C in RT.

Clinical isolates with reduced susceptibility in cell culture to EFV have been obtained. One or more RT substitutions at amino acid positions 98, 100, 101, 103, 106, 108, 188, 190, 225, and 227 were observed in patients failing treatment with EFV in combination with IDV, or with ZDV plus LAM. The substitution K103N was the most frequently observed. Long-term resistance

surveillance (average 52 weeks, range 4 to 106 weeks) analyzed 28 matching baseline and virologic failure isolates. Sixty-one percent (17/28) of these failure isolates had decreased EFV susceptibility in cell culture with a median 88-fold change in EFV susceptibility (EC_{50} value) from reference. The most frequent NNRTI substitution to develop in these patient isolates was K103N (54%). Other NNRTI substitutions that developed included L100I (7%), K101E/Q/R (14%), V108I (11%), G190S/T/A (7%), P225H (18%), and M230I/L (11%).

Cross-Resistance

Cross-resistance among HIV-1 nucleoside analog reverse transcriptase inhibitors (NRTIs) has been observed.

Stavudine: Several studies have demonstrated that prolonged stavudine treatment can select and/or maintain substitutions associated with zidovudine resistance. HIV-1 isolates with one or more zidovudine-resistance-associated substitutions (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) exhibited reduced susceptibility to stavudine in cell culture.

Lamivudine: Lamivudine-resistant HIV-1 mutants were cross resistant to didanosine (ddI) and zalcitabine (ddC). In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple reverse transcriptase inhibitors, including lamivudine, have emerged.

In one clinical study comparing an antiretroviral regimen containing once daily lamivudine to a regimen containing twice daily lamivudine, 53/554 (10%) patients were identified as virological failures (plasma HIV-1 RNA level ≥ 400 copies/mL) by Week 48. Of the 53 failures 28 had been randomized to lamivudine once-daily and 25 to lamivudine twice-daily. Genotypic analysis of on-therapy isolates from 22 patients in the lamivudine twice-daily treatment group showed:

- isolates from 1/22 patients contained treatment-emergent zidovudine resistance-associated substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E)
- isolates from 7/22 contained treatment-emergent efavirenz resistance-associated substitutions (L100I, K101E, K103N, V108I, or Y181C)
- isolates from 5/22 contained treatment-emergent lamivudine resistance-associated substitu tions (M184I or M184V)

Phenotypic analysis of baseline-matched on-therapy HIV-1 isolates from 13 patients receiving lamivudine twice daily showed:

- isolates from all 13 patients were susceptible to zidovudine

- isolates from 3/13 patients exhibited a 21- to 342-fold decrease in susceptibility to efavirenz
- isolates from 4/13 patients exhibited a 29- to 159-fold decrease in susceptibility to lamivudine

Efavirenz: Cross-resistance among NNRTIs has been observed. Clinical isolates previously characterized as EFV-resistant were also phenotypically resistant in cell culture to DLV and NVP compared to baseline. DLV- and/or NVP-resistant clinical viral isolates with NNRTI resistance-associated substitutions (A98G, L100I, K101E/P, K103N/S, V106A, Y181X, Y188X, G190X, P225H, F227L, or M230L) showed reduced susceptibility to EFV in cell culture. Greater than 90% of NRTI-resistant clinical isolates tested retained susceptibility to EFV.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Stavudine and Lamivudine Tablets:

Strides stavudine 40 mg and lamivudine 150 mg dose combination tablets containing 40 mg of stavudine and 150 mg of lamivudine are bioequivalent to Zerit® 40 mg capsules containing 40 mg of stavudine, manufactured by Bristol-Myers Squibb, USA and Epivir® 150 mg tablets containing 150 mg of lamivudine, manufactured by Glaxosmithkline, USA, when administered in a fasted state.

Efavirenz Tablets: Strides co-packaged efavirenz tablets 600 mg are bioequivalent to Sustiva® Tablets containing 600 mg of efavirenz (manufactured by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA) under fasting conditions.

Stavudine:

Absorption: Following oral administration, stavudine is rapidly absorbed, with peak plasma concentrations occurring within 1 hour after dosing. The systemic exposure to stavudine is the same following administration as capsules or solution. Steady-state pharmacokinetic parameters of stavudine in HIV infected adults are shown in Table 1.

Table 1: Steady-State Pharmacokinetic Parameters of stavudine in HIV-Infected Adults	
Parameter	**Stavudine 40 mg BID Mean ±SD (n=8)**
AUC (ng.h/mL)[a]	2568 ± 454
C_{max}(ng/mL)	536 ± 146
C_{min}(ng/mL)	8 ± 9
[a] from 0 to 24 hours AUC = area under the curve over 24 hours. C_{max} = maximum plasma concentration. C_{min} = trough or minimum plasma concentration.	

Distribution: Binding of stavudine to serum proteins was negligible over the concentration range of 0.01 to 11.4 mcg/mL. Stavudine distributes equally between red blood cells and plasma. Volume of distribution is shown in Table 2.

Metabolism: The metabolism of stavudine has not been elucidated in humans.

Elimination: In humans, renal elimination accounts for about 40% of the overall clearance regardless of the route of administration (Table 2). The mean renal clearance was about twice the average endogenous creatinine clearance, indicating active tubular secretion in addition to glomerular filtration. The remaining 60% of the drug is presumably eliminated by endogenous pathways.

Table 2: Pharmacokinetic Parameters of Stavudine in Adult HIV-Infected Patients		
Parameter	**Mean ± SD**	**n**
Oral bioavailability (%)	86.4 ± 18.2	25
Volume of distribution (L)[a]	46 ± 21	44
Total body clearance (mL/min)[a]	594 ± 164	44
Apparent oral clearance (mL/min)[b]	560 ± 182[c]	113
Renal clearance (mL/min)[a]	237 ± 98	39
Elimination half-life, I.V. dose (h)[a]	1.15 ± 0.35	44
Elimination half-life, oral dose (h)[b]	1.6 ± 0.23	8
Urinary recovery of stavudine (% of dose) [a,d]	42 ± 14	39
[a] following 1 hour I.V. infusion.		
[b] following single oral dose.		
[c] assuming body weight of 70 kg		
[d] over 12 – 24 hours		

Lamivudine:

Absorption and distribution: Lamivudine was rapidly absorbed after oral administration in HIV-infected patients. Absolute bioavailability in 12 adult patients was 86% ± 16% (mean ± SD) for the 150-mg tablet. After oral administration of 2 mg/kg twice a day to 9 adults with HIV, the peak serum lamivudine concentration (C_{max}) was 1.5 ± 0.5 mcg/mL (mean ± SD). The area under the plasma concentration versus time curve (AUC) and C_{max} increased in proportion to oral dose over the range from 0.25 to 10 mg/kg.

Distribution: The apparent volume of distribution after IV administration of lamivudine to 20 patients was 1.3 ± 0.4 L/kg, suggesting that lamivudine distributes into extravascular spaces. Volume of distribution was independent of dose and did not correlate with body weight. Binding of lamivudine to human plasma proteins is low (<36%).

Metabolism: Metabolism of lamivudine is a minor route of elimination. In man, the only known metabolite of lamivudine is the trans-sulfoxide metabolite. Within 12 hours after a single oral dose of lamivudine in 6 HIV-infected adults, 5.2% ± 1.4% (mean ± SD) of the dose was excreted as the trans-sulfoxide metabolite in the urine. Serum concentrations of this metabolite have not been determined.

Elimination: The majority of lamivudine is eliminated unchanged in urine by active organic cationic secretion. In 9 healthy subjects given a single 300-mg oral dose of lamivudine, renal clearance was 199.7 ± 56.9 mL/min (mean ± SD). Approximately 70% of an intravenous dose of lamivudine is recovered as unchanged drug in urine. In most single-dose studies in HIV-infected patients, HBV-infected patients, or healthy subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life ($t_{1/2}$) ranged from 5 to 7 hours. In HIV-infected patients, total clearance was 398.5 ± 69.1 mL/min (mean ± SD).

Efavirenz:

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-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 AUC was 184 ± 73 μM•h.

Distrubution: 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 CYP3A4 and CYP2B6 are the major isozymes responsible for efavirenz metabolism.

Efavirenz has been shown to induce P450 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 feces.

Effect of Food on Absorption of Stavudine and Lamivudine Tablets co-packaged with Efavirenz Tablets

The effect of food on the rate and extent of absorption of Stavudine and Lamivudine Tablets co-packaged with Efavirenz Tablets has not been evaluated in a clinical study. Therefore, Stavudine and Lamivudine Tablets co-packaged with Efavirenz Tablets should be taken under fasting conditions.

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** and **PRECAUTIONS: Information for Patients**).

Pharmacokinetics in Special Populations

Impaired Renal Function:

Stavudine and Lamivudine Tablets co-packaged with Efavirenz Tablets are not recommended for patients with impaired renal function (creatinine clearance < 50 mL/min) because Stavudine and Lamivudine Tablets co-packaged with Efavirenz Tablets require dose adjustment in the presence of renal insufficiency.

Impaired Hepatic Function:

Stavudine: Stavudine pharmacokinetics were not altered in five non-HIV-infected patients with hepatic impairment secondary to cirrhosis (Child-Pugh classification B or C) following the administration of a single 40-mg dose.

Lamivudine: The pharmacokinetic properties of lamivudine have been determined in adults with impaired hepatic function. Pharmacokinetic parameters were not altered by diminishing hepatic function; therefore, no dose adjustment for lamivudine is required for patients with impaired hepatic function. Safety and efficacy of lamivudine have not been established in the presence of decompensated liver disease.

Efavirenz: The pharmacokinetics of efavirenz have not been adequately studied in patients with hepatic impairment (see **PRECAUTIONS: General**).

Gender

Stavudine: A population pharmacokinetic analysis of stavudine concentrations collected during a controlled clinical study in HIV-infected patients showed no clinically important differences

between males (n=291) and females (n=27).

Lamivudine: There are no significant gender differences in lamivudine pharmacokinetics.

Efavirenz: The pharmacokinetics of efavirenz in patients appear to be similar between men and women.

Race

Stavudine: A population pharmacokinetic analysis of stavudine concentrations collected during a controlled clinical study in HIV-infected patients showed no clinically important differences associated with race. (233 Caucasian, 39 African American, 41 Hispanic, 1 Asian, and 4 Other)

Lamivudine: There are no significant racial differences in lamivudine pharmacokinetics.

Efavirenz: The pharmacokinetics of efavirenz in patients appear to be similar among the racial groups studied.

Pregnancy: See PRECAUTIONS: Pregnancy

No data are available on pharmacokinetics of stavudine, lamivudine, or efavirenz during pregnancy.

Nursing Mothers: See PRECAUTIONS: Nursing Mothers

Stavudine: No data are available on pharmacokinetics of stavudine in nursing mothers. It is not known whether stavudine is excreted in breast milk.

Lamivudine: Samples of breast milk obtained from 20 mothers receiving lamivudine monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice daily and 300 mg zidovudine twice daily) had measurable concentrations of lamivudine.

Efavirenz: No data are available on pharmacokinetics of efavirenz in nursing mothers. It is not known whether efavirenz is excreted in breast milk.

Pediatric Patients

Stavudine and Lamivudine Tablets co-packaged with Efavirenz Tablets:

The pharmacokinetics of Stavudine and Lamivudine Tablets have not been studied in pediatric patients. Stavudine and Lamivudine Tablets co-packaged with Efavirenz Tablets should not be administered to pediatric patients who weigh less than 60 kg or who are younger than 12 years of age, because adjustments of the dose of Stavudine and Lamivudine co-packaged with Efavirenz Tablets are not possible.

Efavirenz: see **PRECAUTIONS: Pediatric Use**

Geriatric Patients

Stavudine and Lamivudine Tablets: The pharmacokinetics of Stavudine and Lamivudine Tablets have not been studied in patients over 65 years of age. (see **PRECAUTIONS: Geriatric Use).**

Efavirenz: see **PRECAUTIONS: Geriatric Use**

Drug Interactions

Stavudine and Lamivudine:

Ribavirin: In vitro data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n=18), stavudine (n=10), or zidovudine (n=6) were coadministered as part of a multi-drug regimen to HIV/HCV co-infected patients (see **WARNINGS**).

Stavudine: (see **PRECAUTIONS: Drug Interactions)**

Zidovudine: Zidovudine competitively inhibits the intracellular phosphorylation of stavudine. Therefore, use of zidovudine in combination with stavudine should be avoided.

Doxorubicin: In vitro data indicate that the phosphorylation of stavudine is inhibited at relevant concentrations by doxorubicin.

Stavudine does not inhibit the major cytochrome P450 isoforms CYP1A2, CYP2C9, CYP2C19,

CYP2D6, and CYP3A4; therefore, it is unlikely that clinically significant drug interactions will occur with drugs metabolized through these pathways.

Tables 3 and 4 summarize the effects on AUC and Cmax, with a 95% confidence interval (CI) when available, following coadministration of stavudine with didanosine, lamivudine, and nelfinavir. No clinically significant pharmacokinetic interactions were observed.

Table 3: Results of Drug Interaction Studies with Stavudine: Effects of Coadministered Drug on Stavudine Plasma AUC and Cmax Values

Drug	Stavudine Dosage	n[a]	AUC of stavudine (95% CI)	Cmax of stavudine (95% CI)
Didanosine, 100 mg q12h for 4 days	40 mg q12h for 4 days	10	↔	↑ 17%
Lamivudine, 150 mg single dose	40 mg single dose	18	↔ (92.7-100.6%)	↑ 12% (100.3-126.1%)
Nelfinavir, 750 mg q8h for 56 days	30-40 mg q12h for 56 days	8	↔	↔

↑ indicates increase.
↔ indicates no change, or mean increase or decrease of <10%.
[a] HIV-infected patients.

Table 4: Results of Drug Interaction Studies with Stavudine: Effects of Stavudine on Co-administered Drug Plasma AUC and Cmax Values

Drug	Stavudine Dosage	n[a]	AUC of Co-administered Drug (95% CI)	Cmax of Co-administered Drug (95% CI)
Didanosine, 100 mg q12h for 4 days	40 mg q12h for 4 days	10	↔	↔
Lamivudine, 150 mg single dose	40 mg single dose	18	↔ (90.5-107.6%)	↔ (87.1-110.6%)
Nelfinavir, 750 mg q8h for 56 days	30-40 mg q12h for 56 days	8	↔	↔

↔ indicates no change, or mean increase or decrease of <10%.
[a] HIV-infected patients.

Lamivudine: No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-infected adult patients given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg q 12 hr). Other co-administered drugs may alter lamivudine blood concentrations (Table 5) but dose modification is not warranted.

Table 5: Effect of Co-administered Drugs on Lamivudine AUC*

Note: ROUTINE DOSE MODIFICATION OF LAMIVUDINE IS NOT WARRANTED WITH CO-ADMINISTRATION OF THE FOLLOWING DRUGS.

Drugs That May Alter Lamivudine Blood Concentrations					
Coadministered Drug and Dose	**Lamivudine Dose**	**N**	**Lamivudine Concentrations**		**Concentration of Coadministered Drug**
			AUC	**Variability**	
Nelfinavir 750 mg q 8 hr x 7 to 10 days	single 150 mg	11	↑AUC 10%	95% CI: 1% to 20%	↔
Trimethoprim 160 mg/ Sulfamethoxazole 800 mg daily x 5 days	single 300 mg	14	↑AUC 44%	90% CI: 32% to 55%	↔

* This table is not all inclusive.

Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another. Therefore, use of lamivudine in combination with zalcitabine is not recommended.

There was no significant pharmacokinetic interaction between lamivudine and interferon in a study of 19 healthy male subjects.

Efavirenz: Efavirenz has been shown *in vivo* to cause hepatic enzyme induction, thus increasing the biotransformation of some drugs metabolized by CYP3A4. *In vitro* studies have shown that efavirenz inhibited P450 isozymes 2C9, 2C19, and 3A4 with K_i values (8.5-17 μM) in the range of observed efavirenz plasma concentrations. In *in vitro* studies, efavirenz did not inhibit CYP2E1 and inhibited CYP2D6 and CYP1A2 (K_i values 82-160 μM) only at concentrations well above those achieved clinically. The effects on CYP3A4 activity are expected to be similar between 200-mg, 400-mg, and 600-mg doses of efavirenz. Co-administration of efavirenz with drugs primarily metabolized by 2C9, 2C19, and 3A4 isozymes may result in altered plasma concentrations of the co-administered drug. Drugs which induce CYP3A4 activity would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations.

Drug interaction studies were performed with efavirenz and other drugs likely to be co-administered or drugs commonly used as probes for pharmacokinetic interaction. The effects of co-administration of efavirenz on the AUC, C_{max} and C_{min} are summarized in Table 6 (effect of

efavirenz on other drugs) and Table 7 (effect of other drugs on efavirenz). For information regarding clinical recommendations see **PRECAUTIONS: Drug Interactions**.

Table 6: Effect of Efavirenz on Coadministered Drug Plasma C_{max}, AUC, and C_{min}

Co-administered Drug	Dose	Efavirenz Dose	Number of Subjects	Coadministered Drug (mean % change)		
				C_{max} (90% CI)	AUC (90% CI)	C_{min} (90%CI)
Atazanavir	400 mg qd with a light meal d 1-20	600 mg qd with a light meal d 7-20	27	↓ 59% (49-67%)	↓ 74% (68-78%)	↓ 93% (90-95%)
	400 mg qd d 1-6, then 300 mg qd d 7-20 with ritonavir 100 mg qd and a light meal	600 mg qd 2 h after atazanavir and ritonavir d 7-20	13	↑ 14%[a] (↓ 17-↑ 58%)	↑ 39%[a] (2-88%)	↑ 48%[a] (24-76%)
Indinavir	1000 mg q8h x 10 days	600 mg x 10 days	20			
	After morning dose			↔[b]	↓ 33%[b] (26-39%)	↓ 39%[b] (24-51%)
	After afternoon dose			↔[b]	↓ 37%[b] (26-46%)	↓ 52%[b] (47-57%)
	After evening dose			↓ 29%[b] (11-43%)	↓ 46%[b] (37-54%)	↓ 57%[b] (50-63%)
Lopinavir/ ritonavir	400/100 mg q12h x 9 days	600 mg x 9 days	11,7[c]	↔[d]	↓ 19%[d] (↓ 36-↑ 3%)	↓ 39%[d] (3-62%)
Nelfinavir	750 mg q8h x 7 days	600 mg x 7 days	10	↑ 21% (10-33%)	↑ 20% (8-34%)	↔
Metabolite AG-1402				↓ 40% (30-48%)	↓ 37% (25-48%)	↓ 43% (21-59%)
Ritonavir	500 mg q12h x 8 days	600 mg x 10 days	11			
	After AM dose			↑ 24% (12-38%)	↑ 18% (6-33%)	↑ 42% (9-86%)[e]
	After PM dose			↔	↔	↑ 24% (3-50%)[e]
Saquinavir SGC[f]	1200 mg q8h x 10 days	600 mg x 10 days	12	↓ 50% (28-66%)	↓ 62% (45-74%)	↓ 56% (16-77%)[e]
Lamivudine	150 mg q12h x 14 days	600 mg x 14 days	9	↔	↔	↑ 265% (37-873%)
Tenofovir[g]	300 mg qd	600 mg x 14 days	29	↔	↔	↔
Zidovudine	300 mg q12h x 14 days	600 mg x 14 days	9	↔	↔	↑ 225% (43-640%)
Azithromycin	600 mg single dose	400 mg x 7 days	14	↑ 22% (4-42%)	↔	NA

Table 6: Effect of Efavirenz on Coadministered Drug Plasma C_{max}, AUC, and C_{min}

Co-administered Drug	Dose	Efavirenz Dose	Number of Subjects	Coadministered Drug (mean % change) C_{max} (90% CI)	AUC (90% CI)	C_{min} (90%CI)
Clarithromycin	500 mg q12h x 7 days	400 mg x 7 days	11	↓ 26% (15-35%)	↓ 39% (30-46%)	↓ 53% (42-63%)
14-OH metabolite				↑ 49% (32-69%)	↑ 34% (18-53%)	↑ 26% (9-45%)
Fluconazole	200 mg x 7 days	400 mg x 7 days	10	↔	↔	↔
Itraconazole	200 mg q12h x 28 days	600 mg x 14 days	18	↓ 37% (20-51%)	↓ 39% (21-53%)	↓ 44% (27-58%)
Hydroxyitraconazole				↓ 35% (12-52%)	↓ 37% (14-55%)	↓ 43% (18-60%)
Rifabutin	300 mg qd x 14 days	600 mg x 14 days	9	↓ 32% (15-46%)	↓ 38% (28-47%)	↓ 45% (31-56%)
Voriconazole	400 mg po q12h x 1 day then 200 mg po q12h x 8 days	400 mg x 9 days	NA	↓ 61%[h]	↓ 77%[h]	NA
	300 mg po q12h days 2-7	300 mg x 7days		↓36% (21-49%)	↓55% (45-62%)	NA
	400 mg po q12h days 2-7	300 mg x 7 days		↑23% (↓1-↑53%)	↓7% (↓23-↑13%)	NA
Atorvastatin	10 mg qd x 4 days	600 mg x 15 days	14	↓ 14% (1-26%)	↓ 43% (34-50%)	↓ 69% (49-81%)
Total active (including metabolites)				↓ 15% (2-26%)	↓ 32% (21-41%)	↓ 48% (23-64%)
Pravastatin	40 mg qd x 4 days	600 mg x 15 days	13	↓ 32% (↓ 59-↑ 12%)	↓ 44% (26-57%)	↓ 19% (0-35%)
Simvastatin	40 mg qd x 4 days	600 mg x 15 days	14	↓ 72% (63-79%)	↓ 68% (62-73%)	↓ 45% (20-62%)
Total active (including metabolites)				↓ 68% (55-78%)	↓ 60% (52-68%)	NA[i]
Carbamazepine	200 mg qd x 3 days, 200 mg bid x 3 days, then 400 mg qd x 29 days	600 mg x 14 days	12	↓ 20% (15-24%)	↓ 27% (20-33%)	↓ 35% (24-44%)
Epoxide metabolite				↔	↔	↓ 13% (↓ 30-↑ 7%)

Table 6: Effect of Efavirenz on Coadministered Drug Plasma C_{max}, AUC, and C_{min}

Co-administered Drug	Dose	Efavirenz Dose	Number of Subjects	Coadministered Drug (mean % change) C_{max} (90% CI)	AUC (90% CI)	C_{min} (90%CI)
Cetirizine	10 mg single dose	600 mg x 10 days	11	↓ 24% (18-30%)	↔	NA
Diltiazem	240 mg x 21 days	600 mg x 14 days	13	↓ 60% (50-68%)	↓ 69% (55-79%)	↓ 63% (44-75%)
Desacetyl diltiazem				↓ 64% (57-69%)	↓ 75% (59-84%)	↓ 62% (44-75%)
N-monodesmethyl diltiazem				↓ 28% (7-44%)	↓ 37% (17-52%)	↓ 37% (17-52%)
Ethinyl estradiol	50 µg single dose	400 mg x 10 days	13	↔	↑ 37% (25-51%)	NA
Lorazepam	2 mg single dose	600 mg x 10 days	12	↑ 16% (2-32%)	↔	NA
Methadone	Stable maintenance 35-100 mg daily	600 mg x 14-21 days	11	↓ 45% (25-59%)	↓ 52% (33-66%)	NA
Paroxetine	20 mg qd x 14 days	600 mg x 14 days	16	↔	↔	↔
Sertraline	50 mg qd x 14 days	600 mg x 14 days	13	↓ 29% (15-40%)	↓ 39% (27-50%)	↓ 46% (31-58%)

↑ Indicates increase ↓ Indicates decrease ↔ Indicates no change or a mean increase or decrease of <10%.
[a] Compared with atazanavir 400 mg qd alone.
[b] Comparator dose of indinavir was 800 mg q8h x 10 days.
[c] Parallel-group design; n for efavirenz + lopinavir/ritonavir, n for lopinavir/ritonavir alone.
[d] Values are for lopinavir; the pharmacokinetics of ritonavir 100 mg q12h are unaffected by concurrent efavirenz.
[e] 95% CI.
[f] Soft Gelatin Capsule.
[g] Tenofovir disoproxil fumarate.
[h] 90% CI not available.
[i] Not available because of insufficient data.
NA = not available.

Table 7: Effect of Coadministered Drug on Efavirenz Plasma C_{max}, AUC, and C_{min}

Co-administered Drug	Dose	Efavirenz Dose	Number of Subjects	Efavirenz (mean % change) C_{max} (90% CI)	AUC (90% CI)	C_{min} (90%CI)
Indinavir	800 mg q8h x 14 days	200 mg x 14 days	11	↔	↔	↔
Lopinavir/ ritonavir	400/100 mg q12h x 9 days	600 mg x 9 days	11,12[a]	↔	↓ 16% (↓ 38-↑ 15%)	↓ 16% (↓ 42-↑ 20%)
Nelfinavir	750 mg q8h x 7 days	600 mg x 7 days	10	↓ 12% (↓ 32-↑ 13%)[b]	↓ 12% (↓ 35-↑ 18%)[b]	↓ 21% (↓ 53-↑ 33%)

Table 7: Effect of Coadministered Drug on Efavirenz Plasma C_{max}, AUC, and C_{min}

Co-administered Drug	Dose	Efavirenz Dose	Number of Subjects	Efavirenz (mean % change) C_{max} (90% CI)	Efavirenz (mean % change) AUC (90% CI)	Efavirenz (mean % change) C_{min} (90%CI)
Ritonavir	500 mg q12h x 8 days	600 mg x 10 days	9	↑ 14% (4-26%)	↑ 21% (10-34%)	↑ 25% (7-46%)[b]
Saquinavir SGC[c]	1200 mg q8h x 10 days	600 mg x 10 days	13	↓ 13% (5-20%)	↓ 12% (4-19%)	↓ 14% (2-24%)[b]
Tenofovir[d]	300 mg qd	600 mg x 14 days	30	↔	↔	↔
Azithromycin	600 mg single dose	400 mg x 7 days	14	↔	↔	↔
Clarithromycin	500 mg q12h x 7 days	400 mg x 7 days	12	↑ 11% (3-19%)	↔	↔
Fluconazole	200 mg x 7 days	400 mg x 7 days	10	↔	↑ 16% (6-26%)	↑ 22% (5-41%)
Itraconazole	200 mg q12h x 14 days	600 mg x 28 days	16	↔	↔	↔
Rifabutin	300 mg qd x 14 days	600 mg x 14 days	11	↔	↔	↓ 12% (↓ 24-↑ 1%)
Rifampin	600 mg x 7 days	600 mg x 7 days	12	↓ 20% (11-28%)	↓ 26% (15-36%)	↓ 32% (15-46%)
Voriconazole	400 mg po q12h x 1 day then 200 mg po q12h x 8 days	400 mg x 9 days	NA	↑ 38%[e]	↑ 44%[e]	NA
	300 mg po q12h days 2-7	300 mg x 7days		↓14% (7-21%)	↔	NA
	400 mg po q12h days 2-7	300 mg x 7 days		↔	↑17% (6-29%)	NA
Atorvastatin	10 mg qd x 4 days	600 mg x 15 days	14	↔	↔	↔
Pravastatin	40 mg qd x 4 days	600 mg x 15 days	11	↔	↔	↔
Simvastatin	40 mg qd x 4 days	600 mg x 15 days	14	↓ 12% (↓ 28-↑ 8%)	↔	↓ 12% (↓ 25-↑ 3%)
Aluminum hydroxide 400 mg magnesium hydroxide 400 mg, plus simethicone 40 mg	30 mL single dose	400 mg single dose	17	↔	↔	NA
Carbamazepine	200 mg qd x 3 days, 200 mg bid x 3 days, then 400 mg qd x 15 days	600 mg x 35 days	14	↓ 21% (15-26%)	↓ 36% (32-40%)	↓ 47% (41-53%)
Cetirizine	10 mg single dose	600 mg x 10 days	11	↔	↔	↔

Table 7: Effect of Coadministered Drug on Efavirenz Plasma C_{max}, AUC, and C_{min}

Co-administered Drug	Dose	Efavirenz Dose	Number of Subjects	Efavirenz (mean % change) C_{max} (90% CI)	Efavirenz (mean % change) AUC (90% CI)	Efavirenz (mean % change) C_{min} (90%CI)
Diltiazem	240 mg x 14 days	600 mg x 28 days	12	↑ 16% (6-26%)	↑ 11% (5-18%)	↑ 13% (1-26%)
Ethinyl estradiol	50 µg single dose	400 mg x 10 days	13	↔	↔	↔
Famotidine	40 mg single dose	400 mg single dose	17	↔	↔	NA
Paroxetine	20 mg qd x 14 days	600 mg x 14 days	12	↔	↔	↔
Sertraline	50 mg qd x 14 days	600 mg x 14 days	13	↑ 11% (6-16%)	↔	↔

↑ Indicates increase ↓ Indicates decrease ↔ Indicates no change or a mean increase or decrease of <10%.
[a] Parallel-group design; n for efavirenz + lopinavir/ritonavir, n for efavirenz alone.
[b] 95% CI.
[c] Soft Gelatin Capsule.
[d] Tenofovir disoproxil fumarate.
[e] 90% CI not available.

NA = not available.

INDICATIONS AND USAGE

Stavudine and Lamivudine Tablets co-packaged with Efavirenz Tablets are indicated in patients > 12 years of age or those weighing ≥ 60 kg for the treatment of HIV-1 infection.

CONTRAINDICATIONS

Stavudine and Lamivudine Tablets co-packaged with Efavirenz Tablets are contraindicated in patients with clinically significant hypersensitivity to any of the components contained in the tablets.

Efavirenz should not be administered concurrently with astemizole, bepridil, cisapride, midazolam, pimozide, triazolam, or ergot derivatives because competition for CYP3A4 by efavirenz 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). Efavirenz should not be administered concurrently with voriconazole because efavirenz significantly decreases voriconazole plasma concentrations (see **CLINICAL PHARMACOLOGY**, Tables 6 and 7).

WARNINGS

Stavudine and Lamivudine Tablets co-packaged with Efavirenz Tablets should not be administered comcomitantly with formulations containing any of the three drugs. The complete prescribing information for all agents being considered for use with Stavudine and Lamivudine Tablets co-packaged with Efavirenz Tablets should be consulted before combination therapy with stavudine, lamivudine, and efavirenz tablets.

Stavudine and Lamivudine:

Lactic Acidosis/Severe Hepatomegaly with Steatosis: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including stavudine and lamivudine. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering Stavudine and Lamivudine Tablets to any patient with known risk factors for liver disease; however, cases of lactic acidosis have also been reported in patients with no known risk factors.

Treatment with Stavudine and Lamivudine Tablets should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Use with Interferon and Ribavirin-Based Regimens: *In vitro* studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as stavudine and lamivudine. Although no evidence of a pharmacokinetic or pharmacodynamic (e.g., loss of HIV/HCV virologic suppression) interaction was seen when ribavirin was co-administered with stavudine or lamivudine in HIV/HCV co-infected patients (see **CLINICAL PHARMACOLOGY: Drug Interactions**), **hepatic decompensation (some fatal) has occurred in HIV/HCV co-infected patients receiving combination antiretroviral therapy for HIV and interferon with or without ribavirin.** Patients receiving interferon with or without ribavirin and Stavudine and Lamivudine Tablets should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of Stavudine and Lamivudine Tablets co-packaged with Efavirenz Tablets should be considered as medically

appropriate. Dose reduction or discontinuation of interferon, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Childs Pugh >6) (see the complete prescribing information for interferon and ribavirin).

Generalized fatigue, digestive symptoms (nausea, vomiting, abdominal pain, and unexplained weight loss); respiratory symptoms (tachypnea and dyspnea); or neurologic symptoms (including motor weakness, see **Neurologic Symptoms**) might be indicative of the development of symptomatic hyperlactemia or lactic acidosis syndrome. (Note- does this paragrph belong here?)

Stavudine:

Lactic acidosis/Hepatoxicity: Fatal lactic acidosis has been reported in pregnant women who received the combination of stavudine and didanosine with other antiretroviral agents. The combination of stavudine and didanosine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk (see **PRECAUTIONS: Pregnancy**).

An increased risk of hepatotoxicity may occur in patients treated with stavudine in combination with didanosine and hydroxyurea compared to when stavudine is used alone. Deaths attributed to hepatotoxicity have occurred in patients receiving this combination. This combination should be avoided.

Neurologic Symptoms: Motor weakness has been reported rarely in patients receiving combination antiretroviral therapy including stavudine. Most of these cases occurred in the setting of lactic acidosis. The evolution of motor weakness may mimic the clinical presentation of Guillain-Barré syndrome (including respiratory failure). Symptoms may continue or worsen following discontinuation of therapy.

Peripheral neuropathy, manifested by numbness, tingling, or pain in the hands or feet, has been reported in patients receiving stavudine therapy. Peripheral neuropathy has occurred more frequently in patients with advanced HIV disease, with a history of neuropathy, or in patients receiving other drugs that have been associated with neuropathy, including didanosine (see **ADVERSE REACTIONS**)

Pancreatitis: Fatal and nonfatal pancreatitis have occurred during therapy when stavudine was part of a combination regimen that included didanosine, with or without hydroxyurea, in both treatment-naive and treatment-experienced patients, regardless of degree of immunosuppression. The combination of stavudine and didanosine (with or without hydroxyurea) and any other agents that are toxic to the pancreas should be suspended in patients with suspected pancreatitis. Reinstitution of stavudine after a confirmed diagnosis of pancreatitis should be undertaken with particular caution and close patient monitoring. The new regimen should contain neither didanosine nor hydroxyurea.

Lamivudine

In pediatric patients with a history of prior antiretroviral nucleoside exposure, a history of pancreatitis, or other significant risk factors for the development of pancreatitis, lamivudine should be used with caution. Treatment with lamivudine should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur (see ADVERSE REACTIONS).

Post-treatment Exacerbations of Hepatitis: In clinical trials in non-HIV-infected patients treated with lamivudine for chronic hepatitis B, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of lamivudine. These exacerbations have been detected primarily by serum ALT elevations in addition to re-emergence of HBV DNA. Although most events appear to have been self-limited, fatalities have been reported in some cases. Similar events have been reported from post-marketing experience after changes from lamivudine-containing HIV treatment regimens to non-lamivudine-containing regimens in patients infected with both HIV and HBV. The causal relationship to discontinuation of lamivudine treatment is unknown. Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. There is insufficient evidence to determine whether re-initiation of lamivudine alters the course of post-treatment exacerbations of hepatitis.

Efavirenz:

ALERT: Find out about medicines that should NOT be taken with efavirenz. This statement

is also included on the product's bottle labels. (see **CONTRAINDICATIONS** and **PRECAUTIONS: Drug Interactions**.)

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. As with all other non-nucleoside reverse transcriptase inhibitors, 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.

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 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%), nonfatal 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 history of injection drug use, psychiatric history, and receipt of psychiatric medication at study entry; similar associations were observed in both the efavirenz and control treatment groups. In Study 006, onset of new serious psychiatric symptoms occurred throughout the study for both efavirenz-treated and control-treated patients. One percent of efavirenz-treated patients discontinued or interrupted treatment because of one or more of these selected psychiatric symptoms. There have also been occasional postmarketing reports of death by suicide, delusions, and psychosis-like behavior, although a causal relationship to the use of efavirenz cannot be determined from these reports. Patients with serious psychiatric adverse experiences should seek immediate medical evaluation to assess the possibility that the symptoms may be related to the use of efavirenz, and if so, to determine whether the risks of continued therapy outweigh the benefits (see **ADVERSE REACTIONS**).

Nervous System Symptoms: Fifty-three percent of patients receiving efavirenz in controlled trials reported central nervous system symptoms compared to 25% of patients receiving control

regimens. These symptoms included, but were not limited to, dizziness (28.1%), 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: Psychiatric Symptoms**). Dosing at bedtime may improve the tolerability of these nervous system symptoms (see **ADVERSE REACTIONS** and **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.

Drug Interactions: Concomitant use of efavirenz and St. John's wort (*Hypericum perforatum*) or St. John's wort-containing products is not recommended. Coadministration of non-nucleoside reverse transcriptase inhibitors (NNRTIs), including efavirenz, with St. John's wort is expected to substantially decrease NNRTI concentrations and may result in suboptimal levels of efavirenz and lead to loss of virologic response and possible resistance to efavirenz or to the class of NNRTIs.

Reproductive Risk Potential: Pregnancy Category D. Efavirenz may cause fetal harm when administered during the first trimester to a pregnant woman. Pregnancy should be avoided in women receiving efavirenz. Barrier contraception should always be used in combination with other methods of contraception (e.g., oral or other hormonal contraceptives). Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz. If efavirenz is used during the first trimester of pregnancy, or if the patient becomes pregnant while taking efavirenz, the patient should be apprised of the potential harm to the fetus.

There are no adequate and well-controlled studies of efavirenz in pregnant women. Efavirenz should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus, such as in pregnant women without other therapeutic options. As of July 2005, the Antiretroviral Pregnancy Registry has received prospective reports of 282 pregnancies exposed to efavirenz-containing regimens, nearly all of which were first-trimester exposures (277 pregnancies). Birth defects occurred in 5 of 228 live births (first-trimester exposure) and 1 of 14 live births (second/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.

Malformations have been observed in 3 of 20 fetuses/infants from efavirenz-treated cynomolgus monkeys (versus 0 of 20 concomitant controls) in a developmental toxicity study. The pregnant monkeys were dosed throughout pregnancy (postcoital days 20-150) with efavirenz 60 mg/kg daily, a dose which resulted in plasma drug concentrations similar to those in humans given 600 mg/day of efavirenz. Anencephaly and unilateral anophthalmia were observed in one fetus, microophthalmia was observed in another fetus, and cleft palate was observed in a third fetus.

Efavirenz crosses the placenta in cynomolgus monkeys and produces fetal blood concentrations similar to maternal blood concentrations. Efavirenz has been shown to cross the placenta in rats and rabbits and produces fetal blood concentrations of efavirenz similar to maternal

concentrations. An increase in fetal resorptions was observed in rats at efavirenz doses that produced peak plasma concentrations and AUC values in female rats equivalent to or lower than those achieved in humans given 600 mg once daily of efavirenz. Efavirenz produced no reproductive toxicities when given to pregnant rabbits at doses that produced peak plasma concentrations similar to and AUC values approximately half of those achieved in humans given 600 mg once daily of efavirenz.

PRECAUTIONS

Stavudine and Lamivudine Tablets co-packaged with Efavirenz Tablets

Fat Redistribution: 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.

Immune Reconstitution Syndrome: Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including stavudine and lamivudine. 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 necessiate further evaluation and treatment.

Patients With Impaired Renal Function

Stavudine and Lamivudine Tablets co-packaged with Efavirenz Tablets are not recommended for patients with impaired renal function (creatinine clearance <50mL/min) because Stavudine and Lamivudine Tablets co-packaged with Efavirenz Tablets require dose adjustment in the presence of renal insufficiency (see **CLINICAL PHARMACOLOGY)**.

Lamivudine

Patients With HIV and Hepatitis B Virus Coinfection

Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients dually infected with HIV and HBV. In non-HIV-infected patients treated with lamivudine for chronic hepatitis B, emergence of lamivudine-resistant HBV has been detected

and has been associated with diminished treatment response (see EPIVIR-HBV® package insert for additional information).

Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been reported in HIV-infected patients who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus. Post-treatment exacerbations of hepatitis have also been reported (see **WARNINGS**).

Efavirenz

General

Skin Rash: In controlled clinical trials, 26% (266/1008) of patients treated with 600 mg efavirenz experienced new-onset skin rash compared with 17% (111/635) of patients treated in control groups. 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, Stevens-Johnson syndrome) in patients treated with efavirenz in all studies and expanded access was 0.1%. The median time to onset of rash in adults was 11 days and the median duration, 16 days. The discontinuation rate for rash in clinical trials was 1.7% (17/1008). Efavirenz should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement, or fever. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash.

Rash was reported in 26 of 57 pediatric patients (46%) treated with efavirenz capsules. One pediatric patient experienced Grade 3 rash (confluent rash with fever), and two patients had Grade 4 rash (erythema multiforme). The median time to onset of rash in pediatric patients was 8 days. Prophylaxis with appropriate antihistamines prior to initiating therapy with efavirenz in pediatric patients should be considered (see **ADVERSE REACTIONS**).

Liver Enzymes: In patients with known or suspected history of hepatitis B or C infection and in patients treated with other medications associated with liver toxicity, monitoring of liver enzymes is recommended. In patients with persistent elevations of serum transaminases to greater than five times the upper limit of the normal range, the benefit of continued therapy with efavirenz needs to be weighed against the unknown risks of significant liver toxicity (see **ADVERSE REACTIONS: Laboratory Abnormalities**).

Convulsions: Convulsions have been observed infrequently in patients receiving efavirenz, generally in the presence of known medical history of seizures. Patients who are receiving concomitant anticonvulsant medications primarily metabolized by the liver, such as phenytoin, carbamazepine, and phenobarbital, may require periodic monitoring of plasma levels (see **PRECAUTIONS: Drug Interactions)**. Caution must be taken in any patient with a history of seizures.

Animal toxicology: Nonsustained convulsions were observed in 6 of 20 monkeys receiving efavirenz at doses yielding plasma AUC values 4- to 13-fold greater than those in humans given the recommended dose.

Cholesterol: Monitoring of cholesterol and triglycerides should be considered in patients treated with efavirenz (see **ADVERSE REACTIONS**).

Information for Patients

Stavudine and Lamivudine Tablets co-packaged with Efavirenz: Stavudine and Lamivudine Tablets co-packaged with Efavirenz Tablets are for oral ingestion only.

Patients should be advised of the importance of taking Stavudine and Lamivudine co-packaged with Efavirenz Tablets on a regular dosing schedule and to avoid missing doses.

Patients should be advised that Stavudine and Lamividine Tablets co-packaged with Efavirenz Tablets should be taken under fasting conditions.

Patients should be informed that Stavudine and Lamivudine Tablets co-packaged with Efavirenz Tablets are not a cure for HIV-1 infection, and that they may continue to acquire illnesses associated with HIV-1 infection, including opportunistic infections. They should be advised that this combination therapy has not been shown to reduce the risk of transmission of HIV-1 to others through sexual contact or blood contamination.

Patients should be advised to remain under the care of a physician when using Stavudine and Lamivudine co-packaged with Efavirenz Tablets.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time.

Patients should be informed to take Stavudine and Lamivudine Tablets co-packaged with Efavirenz Tablets every day as prescribed. Patients should not alter the dose without consulting their doctor. If a dose is missed, patients should take the next dose as soon as possible. However, if a dose is skipped, the patient should not double the next dose. Patients should be advised to report to their doctor the use of any other medications.

Stavudine

Patients should be informed of the importance of early recognition of symptoms of symptomatic hyperlactatemia or lactic acidosis syndrome, which include unexplained weight loss, abdominal discomfort, nausea, vomiting, fatigue, dyspnea, and motor weakness. Patients in whom these symptoms develop should seek medical attention immediately. Discontinuation of stavudine therapy may be required.

Patients should be informed that an important toxicity of stavudine is peripheral neuropathy. Patients should be aware that peripheral neuropathy is manifested by numbness, tingling, or pain in hands or feet, and that these symptoms should be reported to their physicians. Patients should be counseled that peripheral neuropathy occurs with greatest frequency in patients who have advanced HIV disease or a history of peripheral neuropathy, and that discontinuation of stavudine may be required if toxicity develops.

Caregivers of children receiving stavudine therapy should be instructed regarding detection and reporting of peripheral neuropathy.

Patients should be informed that when stavudine is used in combination with other agents with similar toxicities, the incidence of adverse events may be higher than when stavudine is used alone. An increased risk of pancreatitis, which may be fatal, may occur in patients treated with the combination of stavudine and didanosine, with or without hydroxyurea. Patients treated with this combination should be closely monitored for symptoms of pancreatitis. An increased risk of hepatotoxicity, which may be fatal, may occur in patients treated with stavudine in combination with didanosine and hydroxyurea. This combination should be avoided.

Lamivudine:

Patients should be advised that Stavudine and Lamivudine Tablets co-packaged with Efavirenz Tablets contain a higher dose of the same active ingredient (lamivudine) as EPIVIR-HBV® Tablets and Oral Solution. If a decision is made to include lamivudine in the HIV treatment regimen of a patient dually infected with HIV and HBV, the formulation and dosage of lamivudine in Stavudine and Lamivudine Tablets co-packaged with Efavirenz Tablets (not EPIVIR-HBV®) should be used. In addition, Stavudine and Lamivudine Tablets co-packaged with Efavirenz Tablets should not be administered concomitantly with EPZICOM™, RETROVIR®, or TRIZIVIR® because these products contain the same active ingredient lamivudine.

Patients co-infected with HIV-1 infection and HBV should be informed that deterioration of liver disease has occurred in some cases when treatment with lamivudine was discontinued. Patients should be advised to discuss any changes in regimen with their physician.

Patients should be advised that the long-term effects of lamivudine are unknown at this time. Parents or guardians should be advised to monitor pediatric patients for signs and symptoms of pancreatitis.

Efavirenz:

A statement to patients and healthcare providers is included on the product's bottle labels.

ALERT: Find out about medicines that should NOT be taken with efavirenz. A Patient Package Information (PPI) for efavirenz is available for patient information.

Patients should be advised to take efavirenz every day as prescribed. Efavirenz must always be used in combination with other antiretroviral drugs. Patients should be advised to take efavirenz on an empty stomach, preferably at bedtime. Taking efavirenz with food increases efavirenz concentrations and may increase the frequency of adverse events. Dosing at bedtime may improve the tolerability of nervous system symptoms (see **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**). Patients should remain under the care of a physician while taking efavirenz.

Patients should be informed that central nervous system symptoms including dizziness, insomnia, impaired concentration, drowsiness, and abnormal dreams are commonly reported during the first weeks of therapy with efavirenz. Dosing at bedtime may improve the tolerability of these symptoms, and these symptoms are likely to improve with continued therapy. Patients should be alerted to the potential for additive central nervous system effects when efavirenz is used concomitantly with alcohol or psychoactive drugs. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery (see **WARNINGS: Nervous System Symptoms**). In clinical trials, patients who develop central nervous system symptoms were not more likely to subsequently develop psychiatric symptoms (see **WARNINGS: Psychiatric Symptoms**).

Patients should also be informed that serious psychiatric symptoms including severe depression, suicide attempts, aggressive behavior, delusions, paranoia, and psychosis-like symptoms have also been infrequently reported in patients receiving efavirenz. Patients should be informed that if they experience severe psychiatric adverse experiences they 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 discontinuation of efavirenz may be required. Patients should also inform their physician of any history of mental illness or substance abuse (see **WARNINGS: Psychiatric Symptoms**).

Patients should be informed that another common side effect is rash. These rashes usually go away without any change in treatment. In a small number of patients, rash may be serious. Patients should be advised that they should contact their physician promptly if they develop a rash.

Women receiving efavirenz should be instructed to avoid pregnancy (see **WARNINGS: Reproductive Risk Potential**). A reliable form of barrier contraception should always be used in combination with other methods of contraception, including oral or other hormonal contraception, because the effects of efavirenz on hormonal contraceptives are not fully characterized. Women should be advised to notify their physician if they become pregnant while taking efavirenz. If this drug is used during the first trimester of pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential harm to the

fetus.

Efavirenz may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription, nonprescription medications or herbal products, particularly St. John's wort.

Drug Interactions (see also **CLINICAL PHARMACOLOGY**)

Stavudine:

Zidovudine competitively inhibits the intracellular phosphorylation of stavudine. Therefore, use of zidovudine in combination with stavudine should be avoided.

Lamivudine:

Lamivudine is predominantly eliminated in the urine by active organic cationic secretion. The possibility of interactions with other drugs administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system (e.g., trimethoprim).

Trimethoprim (TMP) 160 mg/sulfamethoxazole (SMX) 800 mg once daily has been shown to increase lamivudine exposure (AUC) by 44%. (see **CLINICAL PHARMACOLOGY).** No change in dose of either drug is recommended. There is no information regarding the effect on lamivudine pharmacokinetics of higher doses of TMP/SMX such as those used to treat Pneumocystis *jirovecii* pneumonia [PCP]. No data are available regarding interactions with other drugs that have renal clearance mechanisms similar to that of lamivudine.

Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another. Therefore, use of lamivudine in combination with zalcitabine is not recommended.

Efavirenz (also see **CONTRAINDICATIONS** and **CLINICAL PHARMCOLOGY: Drug Interactions):**

Efavirenz has been shown *in vivo* to induce CYP3A4. Other compounds that are substrates of

CYP3A4 may have decreased plasma concentrations when co-administered with efavirenz. *In vitro* studies have demonstrated that efavirenz inhibits 2C9, 2C19, and 3A4 isozymes in the range of observed efavirenz plasma concentrations. Co-administration of efavirenz with drugs primarily metabolized by these isozymes may result in altered plasma concentrations of the co-administered drug. Therefore, appropriate dose adjustments may be necessary for these drugs.

Drugs which induce CYP3A4 activity (e.g., phenobarbital, rifampin, rifabutin) would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations. Drug interactions with efavirenz are summarized in Table 8 and 9.

Table 8: Drugs That Are Contraindicated or Not Recommended for Use With Efavirenz

Drug Class: Drug Name	Clinical Comment
Antifungal: voriconazole	CONTRAINDICATED because efavirenz significantly decreases voriconazole plasma concentrations, and coadministration may decrease the therapeutic effectiveness of voriconazole. Also, voriconazole significantly increases efavirenz plasma concentrations, which may increase the risk of efavirenz-associated side effects. The efavirenz 600 mg tablet does not permit the needed dose adjustment. See Tables 5 and 6.
Antihistamine: astemizole	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antimigraine: ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine)	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
Benzodiazepines: midazolam, triazolam	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.
Calcium channel blocker: bepridil	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
GI motility agent: cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Neuroleptic: pimozide	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
St. John's wort (*Hypericum perforatum*)	Expected to substantially decrease plasma levels of efavirenz; has not been studied in combination with efavirenz.

Table 9: Established[a] and Other Potentially Significant[b] Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect on Concentration of Efavirenz or Concomitant Drug	Clinical Comment
Antiretroviral agents		
Protease inhibitor: Amprenavir	↓ amprenavir	Efavirenz has the potential to decrease serum concentrations of amprenavir.
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[a]	When coadministered with efavirenz in treatment-naive patients, the recommended dose of atazanavir is 300 mg with ritonavir 100 mg and efavirenz 600 mg (all once daily). Dosing recommendations for efavirenz and atazanavir in treatment-experienced patients have not been established.
Protease inhibitor: Indinavir	↓ indinavir[a]	The optimal dose of indinavir, when given in combination with efavirenz, is not known. Increasing the indinavir dose to 1000 mg every 8 hours does not compensate for the increased indinavir metabolism due to efavirenz. When indinavir at an increased dose (1000 mg every 8 hours) was given with efavirenz (600 mg once daily), the indinavir AUC and C_{min} were decreased on average by 33-46% and 39-57%, respectively, compared to when indinavir (800 mg every 8 hours) was given alone.
Protease inhibitor: Lopinavir/ritonavir	↓ lopinavir[a]	A dose increase of lopinavir/ritonavir to 533/133 mg (4 capsules or 6.5 mL) twice daily taken with food is recommended when used in combination with efavirenz.
Protease inhibitor: Ritonavir	↑ ritonavir[a] ↑ efavirenz[a]	When ritonavir 500 mg q12h was coadministered with efavirenz 600 mg once daily, the combination was associated with a higher frequency of adverse clinical experiences (eg, dizziness, nausea, paresthesia) and laboratory abnormalities (elevated liver enzymes). Monitoring of liver enzymes is recommended when efavirenz is used in combination with ritonavir.
Protease inhibitor: Saquinavir	↓ saquinavir[a]	Should not be used as sole protease inhibitor in combination with efavirenz.
Other agents		
Anticoagulant: Warfarin	↑ or ↓ warfarin	Plasma concentrations and effects potentially increased or decreased by efavirenz.
Anticonvulsants: Carbamazepine	↓ carbamazepine[a] ↓ efavirenz[a]	There are insufficient data to make a dose recommendation for efavirenz. Alternative anticonvulsant treatment should be used.

Table 9: Established[a] and Other Potentially Significant[b] Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect on Concentration of Efavirenz or Concomitant Drug	Clinical Comment
Phenytoin Phenobarbital	↓ anticonvulsant ↓ efavirenz	Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.
Antidepressant: Sertraline	↓ sertraline[a]	Increased in sertraline dose should be guided by clinical response.
Antifungals:		
Itraconazole	↓ itraconazole[a] ↓ hydroxyitraconazole[a]	Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered.
Ketoconazole	↓ ketoconazole	Drug interaction studies with efavirenz and ketoconazole have not been conducted. efavirenz has the potential to decrease plasma concentrations of ketoconazole.
Anti-infective: Clarithromycin	↓ clarithromycin[a] ↑ 14-OH metabolite[a]	Plasma concentrations decreased by efavirenz; clinical significance unknown. In uninfected volunteers, 46% developed rash while receiving efavirenz and clarithromycin. No dose adjustment of efavirenz is recommended when given with clarithromycin. Alternatives to clarithromycin, such as azithromycin, should be considered (see **Other Drugs**, following table). Other macrolide antibiotics, such as erythromycin, have not been studied in combination with efavirenz.
Antimycobacterial: Rifabutin	↓ rifabutin[a]	Increase daily dose of rifabutin by 50%. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week.
Antimycobacterial: Rifampin	↓ efavirenz[a]	Clinical significance of reduced efavirenz concentrations is unknown. Dosing recommendations for concomitant use of efavirenz and rifampin have not been established.
Calcium channel blockers: Diltiazem	↓ diltiazem[a] ↓ desacetyl diltiazem[a] ↓ N-monodesmethyl diltiazem[a]	Diltiazem dose adjustments should be guided by clinical response (refer to the complete prescribing information for diltiazem). No dose adjustment of efavirenz is necessary when administered with diltiazem.
Others (eg, felodipine, nicardipine, nifedipine, verapamil)	↓ calcium channel blocker	No data are available on the potential interactions of efavirenz with other calcium channel blockers that are substrates of the CYP3A4 enzyme. The potential exists for reduction in plasma concentrations of the calcium channel blocker. Dose adjustments should be guided by clinical response (refer to the complete prescribing information for the calcium channel blocker).
HMG-CoA reductase inhibitors:		Plasma concentrations of atorvastatin, pravastatin, and simvastatin decreased. Consult the complete prescribing information for the HMG-CoA reductase inhibitor for guidance on individualizing the dose.
Atorvastatin	↓ atorvastatin[a]	
Pravastatin	↓ pravastatin[a]	
Simvastatin	↓ simvastatin[a]	

Table 9: Established[a] and Other Potentially Significant[b] Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect on Concentration of Efavirenz or Concomitant Drug	Clinical Comment
Narcotic analgesic: Methadone	↓ methadone[a]	Co-administration in HIV-infected individuals with a history of injection drug use resulted in decreased plasma levels of methadone and signs of opiate withdrawal. Methadone dose was increased by a mean of 22% to alleviate withdrawal symptoms. Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.
Oral contraceptive: Ethinyl estradiol	↑ ethinyl estradiol[a]	Plasma concentrations increased by efavirenz; clinical significance unknown. The potential interaction of efavirenz with oral contraceptives has not been fully characterized. A reliable method of barrier contraception should be used in addition to oral contraceptives.

[a] See **CLINICAL PHARMACOLOGY**, Tables 5 and 6 for magnitude of established interactions.
[b] This table is not all-inclusive.

Other Drugs: Based on the results of drug interaction studies (see Tables 6 and 7), no dosage adjustment is recommended when efavirenz is given with the following: aluminum/magnesium hydroxide antacids, azithromycin, cetirizine, famotidine, fluconazole, lamivudine, lorazepam, nelfinavir, paroxetine, tenofovir disoproxil fumarate, and zidovudine.

Specific drug interaction studies have not been performed with efavirenz and NRTIs other than lamivudine and zidovudine. Clinically significant interactions would not be expected because the NRTIs are metabolized via a different route than efavirenz and would be unlikely to compete for the same metabolic enzymes and elimination pathways.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Stavudine: In 2-year carcinogenicity studies in mice and rats, stavudine was noncarcinogenic at doses which produced exposures (AUC) 39 and 168 times, respectively, human exposure at the recommended clinical dose. Benign and malignant liver tumors in mice and rats and malignant urinary bladder tumors in male rats occurred at levels of exposure 250 (mice) and 732 (rats) times human exposure at the recommended clinical dose.

Stavudine was not mutagenic in the Ames, *E. coli* reverse mutation, or the CHO/HGPRT mammalian cell forward gene mutation assays, with and without metabolic activation. Stavudine produced positive results in the *in vitro* human lymphocyte clastogenesis and mouse fibroblast assays, and in the *in vivo* mouse micronucleus test. In the *in vitro* assays, stavudine elevated the frequency of chromosome aberrations in human lymphocytes (concentrations of 25 to 250 µg/mL, without metabolic activation) and increased the frequency of transformed foci in mouse fibroblast cells (concentrations of 25 to 2500 µg/mL, with and without metabolic activation). In the *in vivo* micronucleus assay, stavudine was clastogenic in bone marrow cells following oral stavudine administration to mice at dosages of 600 to 2000 mg/kg/day for 3 days.
No evidence of impaired fertility was seen in rats with exposures (based on C_{max}) up to 216 times that observed following a clinical dosage of 1 mg/kg/day.

Lamivudine: Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) those observed in humans at the recommended therapeutic dose for HIV infection. Lamivudine was not active in a microbial mutagenicity screen or an *in vitro* cell transformation assay, but showed weak *in vitro* mutagenic activity in a cytogenetic assay using cultured human lymphocytes and in the mouse lymphoma assay. However, lamivudine showed no evidence of *in vivo* genotoxic activity in the rat at oral doses of up to 2,000 mg/kg, producing plasma levels of 35 to 45 times those in humans at the recommended dose for HIV infection. In a study of reproductive performance, lamivudine administered to rats at doses up to 4,000 mg/kg/day, producing plasma levels 47 to 70 times those in humans, revealed no evidence of impaired fertility and no effect on the survival, growth, and development to weaning of the offspring.

Efavirenz: Long-term carcinogenicity studies in mice and rats were carried out with efavirenz. Mice were dosed with 0, 25, 75, 150, or 300 mg/kg/day for 2 years. Incidences of hepatocellular adenomas and carcinomas and pulmonary alveolar/bronchiolar adenomas were increased above background in females. No increases in tumor incidence above background were seen in males. In studies in which rats were administered efavirenz at doses of 0, 25, 50, or 100 mg/kg/day for 2 years, no increases in tumor incidence above background were observed. The systemic exposure (based on AUCs) in mice was approximately 1.7-fold that in humans receiving the 600 mg/day dose. The exposure in rats was lower than that in humans. The mechanism of the carcinogenic

potential is unknown. However, in genetic toxicology assays, efavirenz showed no evidence of mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* studies. These included bacterial mutation assays in *S. typhimurium* and *E. coli*, mammalian mutation assays in Chinese hamster ovary cells, chromosome aberration assays in human peripheral blood lymphocytes or Chinese hamster ovary cells, and an *in vivo* mouse bone marrow micronucleus assay. Given the lack of genotoxic activity of efavirenz, the relevance to humans of neoplasms in efavirenz-treated mice is not known.

Efavirenz did not impair mating or fertility of male or female rats, and did not affect sperm of treated male rats. The reproductive performance of offspring born to female rats given efavirenz was not affected. As a result of the rapid clearance of efavirenz in rats, systemic drug exposures achieved in these studies were equivalent to or below those achieved in humans given therapeutic doses of efavirenz.

Pregnancy

Stavudine and lamivudine are both classified under **Pregnancy Category C.** There are no adequate and well-controlled studies in pregnant women. Lamivudine and Stavudine Tablets co-packaged with Efavirenz Tablets should be used during pregnacy only if the potential benefits outweigh the potential risk.

Pregnancy Category D for efavirenz (see **WARNINGS: Reproductive Risk Potential**).

Stavudine: Reproduction studies have been performed in rats and rabbits with exposures (based on C_{max}) up to 399 and 183 times, respectively, of that seen at a clinical dosage of 1 mg/kg/day and have revealed no evidence of teratogenicity. The incidence in fetuses of a common skeletal variation, unossified or incomplete ossification of sternebra, was increased in rats at 399 times human exposure, while no effect was observed at 216 times human exposure. A slight post-implantation loss was noted at 216 times the human exposure with no effect noted at approximately 135 times the human exposure. An increase in early rat neonatal mortality (birth to 4 days of age) occurred at 399 times the human exposure, while survival of neonates was unaffected at approximately 135 times the human exposure. A study in rats showed that stavudine is transferred to the fetus through the placenta. The concentration in fetal tissue was

approximately one-half the concentration in maternal plasma. Animal reproduction studies are not always predictive of human response.

Fatal lactic acidosis has been reported in pregnant women who received the combination of stavudine and didanosine with other antiretroviral agents. It is unclear if pregnancy augments the risk of lactic acidosis/hepatic steatosis syndrome reported in non-pregnant individuals receiving nucleoside analogues (see **WARNINGS: Lactic Acidosis/Severe Hepatomegaly with Steatosis**). **The combination of stavudine and didanosine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk**. Healthcare providers caring for HIV-infected pregnant women receiving stavudine should be alert for early diagnosis of lactic acidosis/hepatic steatosis syndrome.

Lamivudine: Reproduction studies have been performed in rats and rabbits at orally administered doses up to 4,000 mg/kg/day and 1,000 mg/kg/day, respectively, producing plasma levels up to approximately 35 times that for the adult HIV dose. No evidence of teratogenicity due to lamivudine was observed. Evidence of early embryo lethality was seen in the rabbit at exposure levels similar to those observed in humans, but there was no indication of this effect in the rat at exposure levels up to 35 times that in humans. Studies in pregnant rats and rabbits showed that lamivudine is transferred to the fetus through the placenta.

In 2 clinical studies conducted in South Africa, pharmacokinetic measurements were performed on samples from pregnant women who received lamivudine beginning at Week 38 of gestation (10 women who received 150 mg twice daily in combination with zidovudine and 10 who received lamivudine 300 mg twice daily without other antiretrovirals) or beginning at Week 36 of gestation (16 women who received lamivudine 150 mg twice daily in combination with zidovudine). These studies were not designed or powered to provide efficacy information. Lamivudine pharmacokinetics in the pregnant women were similar to those obtained following birth and in non-pregnant adults. Lamivudine concentrations were generally similar in maternal, neonatal, and cord serum samples. In a subset of subjects from whom amniotic fluid specimens were obtained following natural rupture of membranes, amniotic fluid concentrations of lamivudine ranged from 1.2 to 2.5 mcg/mL (150 mg twice daily) and 2.1 to 5.2 mcg/mL (300 mg

twice daily) and were typically greater than 2 times the maternal serum levels. See the **ADVERSE REACTIONS** section for the limited late-pregnancy safety information available from these studies.

Efavirenz: Pregnancy Category D: See **WARNINGS: Reproductive Risk Potential**.

Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV infection. Additionally, because of the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving Lamivudine and Stavudine Tablets co-packaged with Efavirenz Tablets.

Stavudine: Studies in lactating rats demonstrated that stavudine is excreted in milk. Although it is not known whether stavudine is excreted in human milk, there exists the potential for adverse effects from stavudine in nursing infants.

Lamivudine: A study in lactating rats administered 45 mg/kg of lamivudine showed that lamivudine concentrations in milk were slightly greater than those in plasma. Lamivudine is also excreted in human milk. Samples of breast milk obtained from 20 mothers receiving lamivudine monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice daily and 300 mg zidovudine twice daily) had measurable concentrations of lamivudine.

Efavirenz: Although it is not known if efavirenz is secreted in human milk, efavirenz is secreted into the milk of lactating rats.

Pediatric Use

Stavudine and Lamivudine Tablets co-packaged with Efavirenz Tablets should not be administered to pediatric patients who weigh less than 60 kg or who are younger than 12 years of age, because adjustments of the dose of Stavudine and Lamivudine co-packaged with Efavirenz Tablets are not possible.

Geriatric Use

Stavudine and Lamivudine Tablets co-packaged with Efavirenz Tablets: Clinical studies of Stavudine and Lamivudine Tablets co-packaged with Efavirenz Tablets 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.

Stavudine: In a monotherapy Expanded Access Program for patients with advanced HIV infection, peripheral neuropathy or peripheral neuropathic symptoms were observed in 15 of 40 (38%) elderly patients receiving 40 mg twice daily and 8 of 51 (16%) elderly patients receiving 20 mg twice daily. Of the approximately 12,000 patients enrolled in the Expanded Access Program, peripheral neuropathy or peripheral neuropathic symptoms developed in 30% of patients receiving 40 mg twice daily and 25% of patients receiving 20 mg twice daily. Elderly patients should be closely monitored for signs and symptoms of peripheral neuropathy.

ADVERSE REACTIONS

The adverse events reported with stavudine, lamivudine, and efavirenz are presented below.

Stavudine (Adults): Fatal lactic acidosis has occurred in patients treated with stavudine in combination with other antiretroviral agents. Patients with suspected lactic acidosis should immediately suspend therapy with stavudine. Permanent discontinuation of stavudine should be considered for patients with confirmed lactic acidosis.

Stavudine therapy has rarely been associated with motor weakness, occurring predominantly in the setting of lactic acidosis. If motor weakness develops, stavudine should be discontinued. Stavudine therapy has also been associated with peripheral sensory neuropathy, which can be severe, is dose related, and occurs more frequently in patients being treated with other drugs that have been associated with neuropathy (including didanosine), in patients with advanced HIV infection, or in patients who have previously experienced peripheral neuropathy.

Patients should be monitored for the development of neuropathy, which is usually manifested by numbness, tingling, or pain in the feet or hands. Stavudine-related peripheral neuropathy may resolve if therapy is withdrawn promptly. In some cases, symptoms may worsen temporarily following discontinuation of therapy. If symptoms resolve completely, patients may tolerate resumption of treatment at one-half the dose. If neuropathy recurs after resumption, permanent discontinuation of stavudine should be considered. Stavudine and Lamivudine Tablets co-packaged with Efavirenz Tablets should not be prescribed for patients who require dose reduction due to adverse events.

When stavudine is used in combination with other agents with similar toxicities, the incidence of adverse events may be higher than when stavudine is used alone. Pancreatitis, peripheral neuropathy, and liver function abnormalities occur more frequently in patients treated with the combination of stavudine and didanosine, with or without hydroxyurea. Fatal pancreatitis and hepatotoxicity may occur more frequently in patients treated with stavudine in combination with didanosine and hydroxyurea (see **WARNINGS** and **PRECAUTIONS**).

Selected clinical adverse events that occurred in adult patients receiving stavudine in a controlled monotherapy study are provided in Table 10.

Table 10: Selected Clinical Adverse Events in Monotherapy Study [a]

	Percent (%)	
Adverse Events	Stavudine [b] (40 mg twice daily) (n=412)	Zidovudine (200 mg 3 times daily) (n=402)
Headache	54	49
Diarrhea	50	44
Peripheral Neurologic Symptoms/Neuropathy	52	39
Rash	40	35
Nausea and Vomiting	39	44

[a] Any severity, regardless of relationship to study drug.
[b] Median duration of stavudine therapy = 79 weeks; median duration of zidovudine therapy = 53 weeks.

Pancreatitis was observed in 3 of the 412 adult patients who received stavudine in a controlled monotherapy study.

Selected clinical adverse events that occurred in antiretroviral-naïve adult patients receiving stavudine from two controlled combination studies are provided in Table 11.

Table 11: Selected Clinical Adverse Events[a] in Combination Therapy Studies

	Percent (%)			
	Study		Study 2[b]	
Adverse Events	Stavudine + lamivudine+ indinavir (n=100[c])	Zidovudine+ lamivudine+ indinavir (n=102)	Stavudine + didanosine+ indinavir (n=102[c])	Zidovudine+ lamivudine+ indinavir (n=103)
Nausea	43	63	53	67
Diarrhea	34	16	45	39
Headache	25	26	46	37
Rash	18	13	30	18
Vomiting	18	33	30	35
Peripheral Neurologic Symptoms/Neuropathy	8	7	21	10

[a] Any severity, regardless of relationship to study regimen
[b] Study 2 compared two triple-combination regimens in 205 treatment-naïve patients. Patients received either stavudine (40 mg twice daily) plus didanosine plus indinavir or zidovudine plus lamivudine plus indinavir
[c] Duration of stavudine therapy = 48 weeks.

Pancreatitis resulting in death was observed in patients treated with stavudine plus didanosine, with or without hydroxyurea, in controlled clinical studies and in post-marketing reports.

Selected laboratory abnormalities reported in a controlled monotherapy study are provided in Table 12.

Table 12: Selected Adult Laboratory Abnormalities in Monotherapy Study[a,b]

	Percent (%)	
Parameter	Stavudine (40 mg twice daily) (n=412)	Zidovudine (200 mg 3 times daily) (n=402)
AST (SGOT) (>5 x ULN)	11	10
ALT (SGPT) (>5 x ULN)	13	11
Amylase (≥1.4 x ULN)	14	13

[a] Data presented for patients for whom laboratory evaluations were performed

[b] Median duration of stavudine therapy = 79 weeks; median duration of zidovudine therapy = 53 weeks.

ULN = upper limit of normal.

Selected laboratory abnormalities reported in two-controlled combination studies are provided in Tables 13 and 14.

Table 13: Selected Laboratory Abnormalities in Two Combination Therapy Studies (Grades 3-4)

	Percent (%)			
	Study 1		Study 2	
Parameter	Stavudine + lamivudine+ indinavir (n=100)	Zidovudine+ lamivudine+ indinavir (n=102)	Stavudine + didanosine+ indinavir (n=102)	Zidovudine+ lamivudine+ indinavir (n=103)
Bilirubin (>2.6 x ULN)	7	6	16	8
AST (SGOT) (>5 x ULN)	5	2	7	7
ALT (SGPT) (>5 x ULN)	6	2	8	5
GGT (>5 x ULN)	2	2	5	2
Lipase (>2 x ULN)	6	3	5	5
Amylase (>2 x ULN)	4	<1	8	2

ULN = upper limit of normal.

Table 14: Selected Laboratory Abnormalities in 2 Combination Therapy Studies (All Grades)

	Percent (%)			
	Study 1		Study 2	
Parameter	Stavudine + lamivudine+ indinavir (n=100)	Zidovudine+ lamivudine+ indinavir (n=102)	Stavudine + didanosine+ indinavir (n=102)	Zidovudine+ lamivudine+ indinavir (n=103)
Total Bilirubin	65	60	68	55
AST (SGOT)	42	20	53	20
ALT (SGPT)	40	20	50	18
GGT	15	8	28	12

Lipase	27	12	26	19
Amylase	21	19	31	17

Observed During Clinical Practice

The following events have been identified during post-approval use of stavudine. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to their seriousness, frequency of reporting, causal connection to stavudine, or a combination of these factors.

Body as a Whole - abdominal pain, allergic reaction, chills/fever, and redistribution/accumulation of body fat (see **PRECAUTIONS: Fat Redistribution**).

Digestive Disorders - anorexia.

Exocrine Gland Disorders – pancreatitis [including fatal cases (see **WARNINGS**)].

Hematologic Disorders - anemia, leukopenia, and thrombocytopenia.

Liver – symptomatic hyperlactatemia/lactic acidosis and hepatic steatosis (see **WARNINGS**), hepatitis and liver failure.

Musculoskeletal - myalgia.

Nervous System- insomnia, severe motor weakness (most often reported in the setting of lactic acidosis, see **WARNINGS**).

Lamivudine (Adults):

Clinical Trials in HIV:

Selected clinical adverse events with a ≥5% frequency during therapy with lamivudine 150 mg twice daily plus zidovudine 200 mg 3 times daily compared with zidovudine are listed in Table 15.

Table 15: Selected Clinical Adverse Events (≥5% Frequency) in Four Controlled Clinical Trials (A3001, A3002, B3001, B3002)

Adverse Event	Lamivudine 150 mg Twice Daily Plus zidovudine (n = 251)	zidovudine* (n = 230)
Body as a Whole		
Headache	35%	27%
Malaise & fatigue	27%	23%
Fever or chills	10%	12%

Digestive		
Nausea	33%	29%
Diarrhea	18%	22%
Nausea & vomiting	13%	12%
Anorexia and/or decreased appeptite	10%	7%
Abdominal pain	9%	11%
Abdominal cramps	6%	3%
Dyspepsia	5%	5%
Nervous System		
Neuropathy	12%	10%
Insomnia & other sleep disorders	11%	7%
Dizziness	10%	4%
Depressive disorders	9%	4%
Respiratory		
Nasal signs & symptoms	20%	11%
Cough	18%	13%
Skin		
Skin rashes	9%	6%
Musculoskeletal		
Musculoskeletal pain	12%	10%
Myalgia	8%	6%
Arthralgia	5%	5%

* Either zidovudine monotherapy or zidovudine in combination with zalcitabine.

The types and frequencies of clinical adverse events reported in patients receiving lamivudine 300 mg once daily or lamivudine 150 mg twice daily (in 3-drug combination regimens in EPV 20001 and EPV 40001) were similar. The most common adverse events in both treatment groups were nausea, dizziness, fatigue and/or malaise, headache, dreams, insomnia and other sleep disorders, and skin rash.

Pancreatitis was observed in 9 of the 2,613 adult patients (0.3%) who received lamivudine in the controlled clinical trials EPV20001, NUCA3001, NUCB3001, NUCA3002, NUCB3002, and B3007.

Selected laboratory abnormalities observed during therapy are summarized in Table 16.

Table 16: Frequencies of Selected Laboratory Abnormalities in Adults in Four 24-Week Surrogate Endpoint Studies (A3001, A3002, B3001, B3002) and a Clinical Endpoint Study (B3007)

Test (Threshold Level)	24-Week Surrogate Endpoint Studies*		Clinical Endpoint Study*	
	Lamivudine plus zidovudine	zidovudine †	Lamivudine plus Current Therapy	Placebo plus Current Therapy ‡
Absolute neutrophil count (<750/mm^3)	7.2%	5.4%	15%	13%
Hemoglobin (<8.0 g/dL)	2.9%	1.8%	2.2%	3.4%
Platelets (<50,000/mm^3)	0.4%	1.3%	2.8%	3.8%
ALT (>5.0 x ULN)	3.7%	3.6%	3.8%	1.9%
AST(>5.0 x ULN)	1.7%	1.8%	4.0%	2.1%
Bilirubin (>2.5 x ULN)	0.8%	0.4%	ND	ND
Amylase (>2.0 x ULN)	4.2%	1.5%	2.2%	1.1%

***** The median duration on study was 12 months.
† Either zidovudine monotherapy or zidovudine in combination with zalcitabine.
‡ Current therapy was either zidovudine, zidovudine plus didanosine, or zidovudine plus zalcitabine.
ULN = Upper limit of normal
ND = Not done

In small, uncontrolled studies in which pregnant women were given lamivudine alone or in combination with zidovudine beginning in the last few weeks of pregnancy (see **PRECAUTIONS: Pregnancy**), reported adverse events included anemia, urinary tract infections, and complications of labor and delivery. In post marketing experience, liver function abnormalities and pancreatitis have been reported in women who received lamivudine in combination with other antiretroviral drugs during pregnancy. It is not known whether risks of adverse events associated with lamivudine are altered in pregnant women compared to other HIV-infected patients.

The frequencies of selected laboratory abnormalities reported in patients receiving lamivudine 300 mg once daily or lamivudine 150 mg twice daily (in 3-drug combination regimens in EPV20001 and EPV400001) were similar.

Lamivudine in Patients with Chronic Hepatitis B: Clinical trials in chronic hepatitis B used a lower dose of lamivudine (100 mg daily) than the dose used to treat HIV. The most frequent adverse events with lamivudine versus placebo were ear, nose, and throat infections (25% versus 21%); malaise and fatigue (24% versus 28%); and headache (21% versus 21%), respectively. The most frequent laboratory abnormalities reported with lamivudine were elevated ALT, elevated serum lipase, elevated CPK, and post-treatment elevations of liver function tests. Emergence of HBV viral mutants during lamivudine treatment, associated with reduced drug susceptibility and diminished treatment response, was also reported (see **WARNINGS** and **PRECAUTIONS**). Please see the complete prescribing information for EPIVIR-HBV® Tablets and Oral Solution for more information.

Observed During Clinical Practice: In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of lamivudine. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to lamivudine.

Body as a Whole: Redistribution/accumulation of body fat (see **PRECAUTIONS: Fat Redistribution)**.

Digestive: Stomatitis.

Endocrine and Metabolic: Hyperglycemia.

General: Weakness.

Hemic and Lymphatic: Anemia (including pure red cell aplasia and severe anemias progressing on therapy), lymphadenopathy, splenomegaly.

Hepatic and Pancreatic: Lactic acidosis and hepatic steatosis, pancreatitis, post treatment exacerbation of hepatitis B (see **WARNINGS** and **PRECAUTIONS**).

Hypersensitivity: Anaphylaxis, urticaria.

Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.

Nervous: Paresthesia, peripheral neuropathy.

Respiratory: Abnormal breath sounds/wheezing.
Skin: Alopecia, rash, pruritus.

Efavirenz: The most significant adverse events observed in patients treated with efavirenz are nervous system symptoms, psychiatric symptoms, and rash. Unless otherwise specified, the analyses described below included 1008 patients treated with regimens containing efavirenz and 635 patients treated with a control regimen in controlled trials.

Nervous System Symptoms: Fifty-three percent of patients receiving efavirenz reported central nervous system symptoms (see **WARNINGS: Nervous System Symptoms**). Table 17 lists the frequency of the symptoms of different degrees of severity and gives the discontinuation rates in clinical trials for one or more of the following nervous system symptoms: dizziness, insomnia, impaired concentration, somnolence, abnormal dreaming, euphoria, confusion, agitation, amnesia, hallucinations, stupor, abnormal thinking, and depersonalization. The frequencies of specific central and peripheral nervous system symptoms are provided in Table 19.

Table 17: 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 patient's daily activities.
[d] "Moderate" = Symptoms which may interfere with patient's daily activities.
[e] "Severe" = Events which interrupt patient's usual daily activities.

Psychiatric Symptoms: Serious psychiatric adverse experiences have been reported in patients treated with efavirenz. In controlled trials, the frequency of specific serious psychiatric symptoms among patients who received efavirenz or control regimens, respectively, were severe depression (2.4%, 0.9%), suicidal ideation (0.7%, 0.3%), nonfatal suicide attempts (0.5%, 0),

aggressive behavior (0.4%, 0.5%), paranoid reactions (0.4%, 0.3%), and manic reactions (0.2%, 0.3%) (see **WARNINGS: Psychiatric Symptoms**). Additional psychiatric symptoms observed at a frequency of >2% among patients treated with efavirenz or control regimens, respectively, in controlled clinical trials were depression (19%, 16%), anxiety (13%, 9%), and nervousness (7%, 2%).

Skin Rash: Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first 2 weeks of initiating therapy with efavirenz. In most patients, rash resolves with continuing efavirenz therapy within one month. Efavirenz can be reinitiated in patients interrupting therapy because of rash. Use of appropriate antihistamines and/or corticosteroids may be considered when efavirenz is restarted. Efavirenz should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement, or fever. The frequency of rash by NCI grade and the discontinuation rates as a result of rash are provided in Table 18.

Table 18: Percent of Patients with Treatment-Emergent Rash[a,b]

Percent of Patients with:	**Description of Rash Grade[c]**	**Efavirenz 600 mg Once Daily Adults (n=1008)** %	**Efavirenz Pediatric Patients (n=57)** %	**Control Groups Adults (n= 635)** %
Rash of any grade	—	26.3	45.6	17.5
Grade 1 rash	Erythema, pruritus	10.7	8.8	9.8
Grade 2 rash	Diffuse maculopapular rash, dry desquamation	14.7	31.6	7.4
Grade 3 rash	Vesiculation, moist desquamation, ulceration	0.8	1.8	0.3
Grade 4 rash	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, necrosis requiring surgery, exfoliative dermatitis	0.1	3.5	0.0
Treatment	—	1.7	8.8	0.3

discontinuation as a result of rash				

[a] Includes events reported regardless of causality.
[b] Data from Study 006 and three Phase 2/3 studies.
[c] NCI Grading System.

As seen in Table 18, rash is more common in pediatric patients and more often of higher grade (i.e., more severe) (see **PRECAUTIONS: General**).

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.

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 **ADVERSE REACTIONS: Laboratory Abnormalities**).

Selected clinical adverse experiences of moderate or severe intensity observed in ≥2% of efavirenz-treated patients in two controlled clinical trials are presented in Table 19.

Table 19: Selected Treatment-Emergent[a] Adverse Events of Moderate or Severe Intensity Reported in ≥2% of Efavirenz-Treated Patients in Studies 006 and ACTG 364

Adverse Events	**Study 006 LAM-, NNRTI-, and Protease Inhibitor-Naive Patients**			**Study ACTG 364 NRTI-experienced, NNRTI- and Protease Inhibitor-Naive Patients**		
	Efavirenz[b] + ZDV/LAM (n=412)	Efavirenz[b] + Indinavir (n=415)	Indinavir + ZDV/LAM (n=401)	Efavirenz[b] + Nelfinavir + NRTIs (n=64)	Efavirenz[b] + NRTIs (n=65)	Nelfinavir + NRTIs (n=66)
	180 weeks[c]	102 weeks[c]	76 weeks[c]	71.1 weeks[c]	70.9 weeks[c]	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 & Appendages						
Rash	11%	16%	5%	9%	5%	9%
Pruritus	<1%	1%	1%	9%	5%	9%

[a] Includes adverse events at least possibly related to 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.
— = Not Specified.
ZDV = zidovudine, LAM=lamivudine.

Clinical adverse experiences observed in ≥10% of 57 pediatric patients aged 3 to 16 years who received efavirenz capsules, nelfinavir, and one or more NRTIs were: rash (46%), diarrhea/loose stools (39%), fever (21%), cough (16%), dizziness/lightheaded/fainting (16%), ache/pain/discomfort (14%), nausea/vomiting (12%), and headache (11%). The incidence of nervous system symptoms was 18% (10/57). One patient experienced Grade 3 rash, two patients had Grade 4 rash, and five patients (9%) discontinued because of rash (see also **PRECAUTIONS: Skin Rash** and **Pediatric Use**).

Postmarketing Experience-efavirenz

Body as a Whole - allergic reactions, asthenia, redistribution/accumulation of body fat (see **PRECAUTIONS: Fat Redistribution**).

Central and Peripheral Nervous System -abnormal coordination, ataxia, convulsions, hypoesthesia, paresthesia, neuropathy, tremor.

Endocrine -gynecomastia.

Gastrointestinal - constipation, malabsorption.

Cardiovascular - flushing, palpitations.

Liver and Biliary System - hepatic enzyme increase, hepatic failure, hepatitis.

Metabolic and Nutritional -hypercholesterolemia, hypertriglyceridemia.

Musculoskeletal - arthralgia, myalgia, myopathy.

Psychiatric -aggressive reactions, agitation, delusions, emotional lability, mania, neurosis, paranoia, psychosis, suicide.

Respiratory -dyspnea.

Skin and Appendages -erythema multiforme, nail disorders, photoallergic dermatitis, skin discoloration, Stevens-Johnson syndrome.

Special Senses -abnormal vision, tinnitus.

Laboratory Abnormalities

Selected Grade 3-4 laboratory abnormalities reported in ≥2% of efavirenz-treated patients in two clinical trials are presented in Table 20.

Table 20: Selected Grade 3-4 Laboratory Abnormalities 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**		
Variable	Limit	Efavirenz[a] + ZDV/LAM (n=412) 180 weeks[b]	Efavirenz[a] + Indinavir (n=415) 102 weeks[b]	Indinavir + ZDV/LAM (n=401) 76 weeks[b]	Efavirenz[a] + Nelfinavir + NRTIs (n=64) 71.1 weeks[b]	Efavirenz[a] + NRTIs (n=65) 70.9 weeks[b]	Nelfinavir + NRTIs (n=66) 62.7 weeks[b]

Chemistry							
ALT	>5 x ULN	5%	8%	5%	2%	6%	3%
AST	>5 x ULN	5%	6%	5%	6%	8%	8%
GGT[c]	>5 x ULN	8%	7%	3%	5%	0	5%
Amylase	>2 x 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/mm^3	10%	3%	5%	2%	3%	2%

[a] Efavirenz provided as 600 mg once daily.
[b] Median duration of treatment.
[c] Isolated elevations of GGT in patients receiving efavirenz may reflect enzyme induction not associated with liver toxicity.
[d] Nonfasting.
ZDV = zidovudine, LAM = lamivudine. ULN = Upper limit of normal. ALT = alanine aminotransferase. AST = aspartate aminotransferase. GGT = gamma-glutamyltransferase.

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

Lipids: Increases from baseline in total cholesterol of 10-20% have been observed in some uninfected volunteers receiving efavirenz. In patients treated with efavirenz + zidovudine + lamivudine, increases from baseline in nonfasting total cholesterol and HDL of approximately 20% and 25%, respectively, were observed. In patients treated with efavirenz + indinavir, increases from baseline in nonfasting cholesterol and HDL of approximately 40% and 35%, respectively, were observed. Nonfasting total cholesterol levels ≥240 mg/dL 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%, respectively, of patients treated with indinavir + zidovudine + lamivudine. The effects of efavirenz on triglycerides and LDL were not well characterized because samples were taken from nonfasting patients. The clinical significance of these findings is unknown (see **PRECAUTIONS: General**).

***Cannabinoid Test Interaction*:** Efavirenz does not bind to cannabinoid receptors. False-positive urine cannabinoid test results have been observed in non-HIV-infected volunteers receiving efavirenz when the Microgenics CEDIA® DAU Multi-Level THC assay was used for screening. Negative results were obtained when more specific confirmatory testing was performed with gas chromatography/mass spectrometry.

Of the three assays analyzed (Microgenics CEDIA DAU Multi-Level THC assay, Cannabinoid Enzyme Immunoassay [Diagnostic Reagents, Inc], and AxSYM® Cannabinoid Assay), only the Microgenics CEDIA DAU Multi-Level THC assay showed false-positive results. The other two assays provided true-negative results. The effects of efavirenz on cannabinoid screening tests other than these three are unknown. The manufacturers of cannabinoid assays should be contacted for additional information regarding the use of their assays with patients receiving efavirenz.

OVERDOSAGE

Stavudine and Lamivudine Tablets co-packaged with Efavirenz Tablets: There is no known antidote for stavudine, lamivudine, or efavirenz.

Stavudine: Experience with adults treated with 12 to 24 times the recommended daily dosage revealed no acute toxicity. Complications of chronic overdosage include peripheral neuropathy and hepatic toxicity. Stavudine can be removed by hemodialysis; the mean ± SD hemodialysis clearance of stavudine is 120 ± 18 mL/min. Whether stavudine is eliminated by peritoneal dialysis has not been studied.

Lamivudine: One case of an adult ingesting 6 g of lamivudine was reported; there were no clinical signs or symptoms noted and hematologic tests remained normal. Two cases of pediatric overdose were reported in ACTG300. One case was a single dose of 7 mg/kg of lamivudine; the

second case involved use of 5 mg/kg of lamivudine twice daily for 30 days. There were no clinical signs or symptoms noted in either case. Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event. If overdose occurs, the patient should be monitored, and standard supportive treatment applied as required.

Efavirenz: Some patients accidentally taking 600 mg twice daily have reported increased nervous system symptoms. One patient experienced involuntary muscle contractions.
Treatment of overdose with efavirenz should consist of general supportive measures, including monitoring of vital signs and observation of the patient's clinical status. Administration of activated charcoal may be used to aid removal of unabsorbed drug. There is no specific antidote for overdose with efavirenz. Because efavirenz is highly protein bound, dialysis is unlikely to significantly remove the drug from blood.

DOSAGE AND ADMINISTRATION

The effect of food on the absorption Stavudine and Lamivudine Tablets co-packaged with Efavirenz Tablets have not been evaluated in a clinical study. Therefore, Stavudine and Lamivudine Tablets co-packaged with Efavirenz Tablets should be taken under fasting conditions.

Adults and Adolescents:

Stavudine and Lamivudine Tablets: The recommended oral dose for adults and adolescents (> 12 years of age) who weigh ≥ 60 kg is one Stavudine and Lamivudine (40 mg/ 150 mg) Tablet taken twice daily on an empty stomach.
Stavudine and Lamivudine Tablets should be taken at intervals of 12 hours.

(Note- format for d4T/3TC and EFV wording are different)

Efavirenz Tablets: The recommended dose is one tablet (600 mg) taken once daily on an empty stomach, preferably at bedtime. The increased efavirenz concentrations observed following administration of efavirenz with food may lead to an increase in frequency of adverse events (see **CLINICAL PHARMACOLOGY: Effect of Food on Oral Absorption**). Dosing at bedtime may improve the tolerability of nervous system symptoms (see **WARNINGS: Nervous System Symptoms**, **PRECAUTIONS: Information for Patients**, and **ADVERSE REACTIONS**).

Pediatrics

Stavudine and Lamivudine Tablets co-packaged with Efavirenz Tablets are not recommended for pediatric patients < 12 years of age or those who weigh < 60 kg.

Dosage Adjustment

Stavudine and Lamivudine Tablets co-packaged with Efavirenz Tablets are not recommended for patients requiring dosage adjustment, such as those with reduced renal function (creatinine clearance ≤50 ml/min) and those experiencing dose-limiting adverse events.

HOW SUPPLIED

Stavudine 40mg and Lamivudine 150mg dose combination tablet, is a light pink to pink colored, circular, flat bevel edged tablets with LS40 engraved on one side and plain on other side. 60 tablets are packed in 50ml HDPE container with tear-off cap.

Efavirenz Tablets 600 mg are off white colored, capsular-shaped, film-coated tablets, plain on one side and break line on other side. 30 tablets are packed in 50ml HDPE container with tear-off cap with EPE (Expanded Polyethylene) Foam filler..

One container of each is co-packaged in a printed paperboard carton.

Storage

Stavudine 40 mg and Lamivudine 150 mg Tablets:

Store at 20° to 25° C (68° to 77° F) [See USP Controlled Room Temperature]. Protect from light. Keep all medicines away from children.

Efavirenz Tablets:

Efavirenz tablets should be stored at 20° to 25° C (68° to 77° F) [See USP Controlled Room Temperature]. Keep all medicines away from children.

Manufactured by:

STRIDES ARCOLAB LIMITED,

Bangalore- India.