PRESCRIBING INFORMATION

Lamivudine 150 mg/Zidovudine 300 mg Tablets Co-Packaged

with Efavirenz 600 mg Tablets

R_X only

WARNINGS:

ZIDOVUDINE HAS BEEN ASSOCIATED WITH HEMATOLOGIC TOXICITY INCLUDING NEUTROPENIA AND SEVERE ANEMIA, PARTICULARLY IN PATIENTS WITH ADVANCED HIV DISEASE (SEE WARINIGS). PROLONGED USE OF ZIDOVUDINE HAS BEEN ASSOCIATED WITH SYMPTOMATIC MYOPATHY.

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING LAMIVUDINE, ZIDOVUDINE AND OTHER ANTIRETROVIRALS (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, WHICH IS ONE COMPONENT OF LAMIVUDINE/ZIDOVUDINE TABLETS. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE LAMIVUDINE/ZIDOVUDINE TABLETS AND ARE CO-INFECTED WITH HIV AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS).

DESCRIPTION

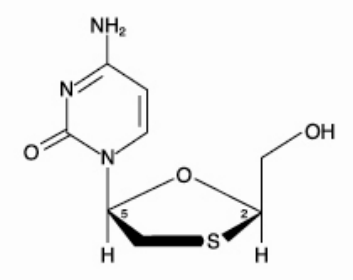
Lamivudine/Zidovudine Tablets:

Lamivudine/zidovudine Tablets are combination tablets containing lamivudine and zidovudine. Lamivudine and zidovudine are synthetic nucleoside analogues with activity against HIV.

The lamivudine/zidovudine Tablets are for oral administration. Each lamivudine/zidovudine Tablet contains the active ingredients 150 mg of lamivudine, 300 mg of zidovudine, and the

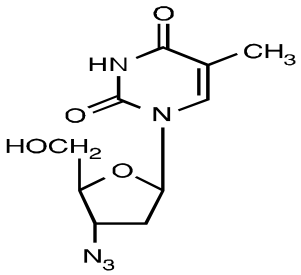
inactive ingredients microcrystalline cellulose, sodium starch glycolate, povidone, colloidal silicon dioxide, talc, magnesium stearate, color Opadry white (Y-1-7000), purified water and isopropyl alcohol. Opadry white contains Hydroxy Propyl Methylcellulose 2910/ Hypromellose 5cP, Titanium dioxide, Polyethylene glycol 400 (Macrogol).

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 a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.26. It has the following structural formula:



Lamivudine is a white to off-white crystalline solid with a solubility of approximately 70 mg/mL in water at 20°C.

Zidovudine: The chemical name of zidovudine is 3'-azido-3'-deoxythymidine. It has a molecular formula of $C_{10}H_{13}N_5O_4$ and a molecular weight of 267.24. It has the following structural formula:



Zidovudine is a white to beige, odorless, crystalline solid with a solubility of 20.1 mg/mL in water at 25°C.

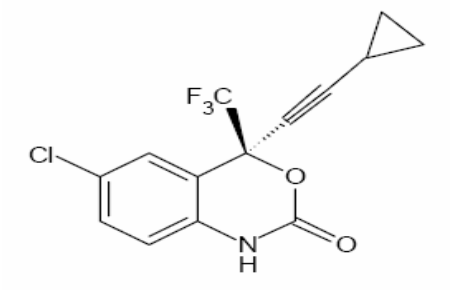
Efavirenz Tablets:

Efavirenz is a human immunodeficiency virus type 1 (HIV-1) specific, non-nucleoside, reverse transcriptase inhibitor (NNRTI).

Efavirenz is available as film-coated tablets for oral administration containing 600 mg of efavirenz and the following 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.

Efavirenz is chemically described as (S)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one.

Its empirical formula is $C_{14}H_9ClF_3NO_2$ and its structural formula is:



Efavirenz is a white to slightly pink crystalline powder with a molecular mass of 315.68. It is practically insoluble in water (<10 µg/mL).

MICROBIOLOGY:

Mechanism of Action:

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 cellular DNA polymerases α, β and γ.

Zidovudine: Zidovudine is a synthetic nucleoside analogue. Intracellularly, zidovudine is phosphorylated to its active 5′-triphosphate metabolite, zidovudine triphosphate (ZDV-TP). The prinicipal mode of action of ZDV-TP is inhibition of RT via DNA chain termination after incorporation of the nucleotide analogue. ZDV-TP is a weak inhibitor of the cellular DNA polymerase α and γ and has been reported to be incorporated into the DNA of cells in culture.

Efavirenz: Efavirenz (EFV) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1). EFV activity is mediated predominantly by noncompetitive

inhibition of HIV-1 reverse transcriptase (RT). HIV-2 RT and human cellular DNA polymerases α, β, γ, and δ are not inhibited by EFV.

Antiviral Activity:

Lamivudine/Zidovudine: In HIV-1–infected MT-4 cells, lamivudine in combination with zidovudine at various ratios had synergistic antiretroviral activity.

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 (1μM = 0.23 mcg/mL). HIV from therapy-naive subjects with no mutations associated with resistance gave median EC_{50} values of 0.426 μM (range: 0.200 to 2.007 μM) from Virco (n = 93 baseline samples from COLA40263) and 2.35 μM (1.44 to 4.08 μM) from Monogram Biosciences (n = 135 baseline samples from ESS30009). 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 in peripheral blood mononuclear cells. Ribavirin (50μM) decreased the anti-HIV-1 activity of lamivudine by 3.5 fold in MT-4 cells.

Zidovudine: The antiviral activity of zidovudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes). The EC_{50} and EC_{90} values for zidovudine were 0.01 to 0.49 μM (1 μM = 0.27 mcg/mL) and 0.1 to 9 μM, respectively. HIV from therapy-naive subjects with no mutations associated with resistance gave median EC_{50} values of 0.011 μM (range: 0.005 to 0.110 μM) from Virco (n = 93 baseline samples from COLA40263) and 0.02 μM (0.01 to 0.03 μM) from Monogram Biosciences (n = 135 baseline samples from ESS30009). The EC_{50} values of zidovudine against different HIV-1 clades (A-G) ranged from 0.00018 to 0.02 μM, and against HIV-2 isolates from 0.00049 to 0.004 μM. In cell culture drug combination studies, zidovudine demonstrates synergistic activity with the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir, didanosine, lamivudine, and zalcitabine; the non-nucleoside reverse transcriptase inhibitors (NNRTIs) delavirdine and nevirapine; and the protease inhibitors (PIs) indinavir, nelfinavir, ritonavir, and saquinavir; and additive activity with interferon alfa. Ribavirin has been found to inhibit the phosphorylation of zidovudine in cell culture.

Efavirenz: The concentration of EFV inhibiting *in vitro* replication of wild-type laboratory adapted strains and clinical isolates by 90-95% (IC_{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 vitro* 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:

Lamivudine/Zidovudine Administered As Separate Formulations: 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.

HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from patients after prolonged lamivudine/zidovudine therapy. Dual resistance required the presence of multiple mutations, the most essential of which may be G333E. The incidence of dual resistance and the duration of combination therapy required before dual resistance occurs are unknown.

Lamivudine: Lamivudine-resistant isolates of HIV-1 have been selected in cell culture and have also been recovered from patients treated with lamivudine or lamivudine plus zidovudine. Genotypic analysis of the resistant isolates selected in cell cultures and recovered from lamivudine-treated patients showed that the resistance was due to a specific amino acid substitution in the HIV-1 reverse transcriptase at codon 184 changing the methionine to either isoleucine or valine (M184V/I).

Mutations 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, HBV 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**).

Zidovudine: HIV isolates with reduced susceptibility to zidovudine have been selected in cell culture and were also recovered from patients treated with zidovudine. Genotypic analyses of the isolates selected in cell cultures and recovered from zidovudine-treated patients showed mutations in the HIV-1 RT gene resulting in 6 amino acid substitutions (M41L, D67N, K70R, L210W, T215Y or F, and K219Q) that confer zidovudine resistance. In general, higher levels of resistance were associated with greater number of mutations.

Efavirenz: HIV-1 isolates with reduced susceptibility to EFV (>380-fold increase in IC_{90} value) emerged rapidly under *in vitro* 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 vitro* 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 mutation K103N was the most frequently observed. Long-term resistance surveillance (average 52 weeks, range 4-106 weeks) analyzed 28 matching baseline and virologic failure isolates. Sixty-one percent (17/28) of these failure isolates had decreased EFV susceptibility *in vitro* with a median 88-fold change in EFV susceptibility (IC_{50} value) from reference. The most frequent NNRTI mutation to develop in these patient isolates was K103N (54%). Other NNRTI mutations 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 has been observed among NRTIs.

Lamivudine/Zidovudine: Cross-resistance between lamivudine and zidovudine has not been reported. In some patients treated with lamivudine alone or in combination with zidovudine, isolates have emerged with a mutation at codon 184, which confers resistance to lamivudine. Cross-resistance to abacavir, didanosine, tenofovir, and zalcitabine has been observed in some patients harboring lamivudine-resistant HIV-1 isolates. In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple drugs, including lamivudine, have emerged (see under Zidovudine below).

Lamivudine: See Lamivudine Plus Zidovudine (above).

Zidovudine: In a study of 167 HIV-infected patients, isolates (n = 2) with multi-drug resistance to didanosine, lamivudine, stavudine, zalcitabine, and zidovudine were recovered from patients treated for ≥1 year with zidovudine plus didanosine or zidovudine plus zalcitabine. The pattern of resistance-associated mutations with such combination therapies was different (A62V, V75I, F77L, F116Y, Q151M) from the pattern with zidovudine monotherapy, with the Q151M mutation being most commonly associated with multi-drug resistance. The mutation at codon 151 in combination with mutations at 62, 75, 77, and 116 results in a virus with reduced susceptibility to didanosine, lamivudine, stavudine, zalcitabine, and zidovudine. Thymidine analogue mutations (TAMs) are selected by zidovudine and confer cross-resistance to abacavir, didanosine, stavudine, tenofovir, and zalcitabine.

Efavirenz: Cross-resistance among NNRTIs has been observed. Clinical isolates previously characterized as EFV-resistant were also phenotypically resistant *in vitro* 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 vitro*. Greater than 90% of NRTI-resistant clinical isolates tested *in vitro* retained susceptibility to EFV.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS IN ADULTS:

Lamivudine/Zidovudine Tablet: Strides Lamivudine 150 mg/Zidovudine 300 mg Tablets containing lamivudine 150 mg and zidovudine 300 mg are bioequivalent to Combivir® tablets containing lamivudine 150 mg / zidovudine 300 mg (manufactured by GlaxoSmithKline, Research Triangle Park, NC 27709. USA) when administered in a fasted state.

Efavirenz Tablet: Strides co-packaged efavirenz tablet containing 600 mg of efavirenz is bioequivalent to Sustiva® Tablet containing 600 mg of Efavirenz (manufactured by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA), under fasting condition.

Lamivudine: The pharmacokinetic properties of lamivudine in fasting patients are summarized in Table 1. Following oral administration, lamivudine is rapidly absorbed and extensively distributed. Binding to plasma protein is low. Approximately 70% of an intravenous dose of lamivudine is recovered as unchanged drug in the urine. Metabolism of lamivudine is a minor route of elimination. In humans, the only known metabolite is the trans-sulfoxide metabolite

(approximately 5% of an oral dose after 12 hours). Serum concentrations of this metabolite have not been determined.

Zidovudine: The pharmacokinetic properties of zidovudine in fasting patients are summarized in Table 1. Following oral administration, zidovudine is rapidly absorbed and extensively distributed. Binding to plasma protein is low. Zidovudine is eliminated primarily by hepatic metabolism. The major metabolite of zidovudine is 3′-azido-3′-deoxy-5′-O-β-D-glucopyranuronosylthymidine (GZDV). GZDV area under the curve (AUC) is about 3-fold greater than the zidovudine AUC. Urinary recovery of zidovudine and GZDV accounts for 14% and 74% of the dose following oral administration, respectively. A second metabolite, 3′-amino-3′-deoxythymidine (AMT), has been identified in plasma. The AMT AUC was one fifth of the zidovudine AUC.

Table 1: Pharmacokinetic Parameters* for Lamivudine and Zidovudine in Adults

Parameter	Lamivudine		Zidovudine	
Oral bioavailability (%)	86 ± 16	n = 12	64 ± 10	n = 5
Apparent volume of distribution (L/kg)	1.3 ± 0.4	n = 20	1.6 ± 0.6	n = 8
Plasma protein binding (%)	<36		<38	
CSF: plasma ratio†	0.12 [0.04 to 0.47]	n= 38‡	0.60 [0.04 to 2.62]	n = 39§
Systemic clearance (L/hr/kg)	0.33 ± 0.06	n = 20	1.6 ± 0.6	n = 6
Renal clearance (L/hr/kg)	0.22 ± 0.06	n = 20	0.34 ± 0.05	n = 9
Elimination half-life (hr) ||	5 to 7		0.5 to 3	

* Data presented as mean ± standard deviation except where noted.
†Median [range].
‡ Children.
§ Adults.
|| Approximate range.

Efavirenz:

Absorption and bioavailability:

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.

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

Metabolism: Studies in humans and *in vitro* studies using human liver microsomes have demonstrated that efavirenz is principally metabolized by the cytochrome P450 system to hydroxylated metabolites with subsequent glucuronidation of these hydroxylated metabolites. These metabolites are essentially inactive against HIV-1. The *in vitro* studies suggest that 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 Lamivudine/Zidovudine Co-Packaged with Efavirenz Tablets: The effect of food was not assessed for the lamivudine/zidovudine tablets co-packaged with efavirenz tablets. Therefore, lamivudine/zidovudine tablets co-packaged with efavirenz tablets should be taken under fasted conditions.

Effect of Food on Absorption of Efavirenz: Administration of a single 600-mg efavirenz (Sustiva) 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 Population

Renal Impairment:

Lamivudine/zidovudine tablets co-packaged with efavirenz tablets are not recommended for patients with impaired renal function (creatinine clearance <50 mL/min) because lamivudine/zidovudine Tablets require dose adjustment in the presence of renal insufficiency. (see PRECAUTIONS and DOSAGE and ADMINISTRATION).

Hepatic Impairment:

A reduction in the daily dose of zidovudine may be necessary in patients with mild to moderate impaired hepatic function or liver cirrhosis. Lamivudine/zidovudine Tablets co-packaged with efavirenz tablets are not recommended for patients with impaired hepatic function because dose adjustments are not possible

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

Gender

Lamivudine and zidovudine: A pharmacokinetic study in healthy male (n = 12) and female (n = 12) subjects showed no gender differences in zidovudine exposure (AUC_∞) or lamivudine AUC_∞ normalized for body weight

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

Race

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

Zidovudine: The pharmacokinetics of zidovudine with respect to race have not been determined.

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

Pediatric Patients

The Lamivudine 150 mg/Zidovudine 300 mg Tablets co-packaged with Efavirenz 600 mg Tablets combination should not be used in the subjects < 12 years of age and those weighing <40kg.

Geriatric Patients

The Lamivudine 150 mg/Zidovudine 300 mg Tablets co-packaged with Efavirenz 600 mg Tablets combination have not been studied in patients > 65 years of age (see **PRECAUTIONS**).

Pregnancy: See **PRECAUTIONS**

Lamivudine and efavirenz: No data available.

Zidovudine: Zidovudine pharmacokinetics have been studied in a Phase 1 study of 8 women during the last trimester of pregnancy. As pregnancy progressed, there was no evidence of drug accumulation. The pharmacokinetics of zidovudine were similar to that of nonpregnant adults. Consistent with passive transmission of the drug across the placenta, zidovudine concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at delivery. Although data are limited, methadone maintenance therapy in 5 pregnant women did not appear to alter zidovudine pharmacokinetics. In a nonpregnant adult population, a potential for interaction has been identified (see CLINICAL PHARMACOLOGY: Drug Interactions).

Efavirenz: See **WARNINGS: Reproductive Risk Potential**

Nursing mothers: See **PRECAUTIONS: Nursing Mothers**

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.

Zidovudine: After administration of a single dose of 200 mg zidovudine to 13 HIV-infected women, the mean concentration of zidovudine was similar in human milk and serum.

Efavirenz: See **PRECAUTIONS: Nursing Mothers**

Drug Interactions: (See also **PRECAUTIONS: Drug Interactions)**

Lamivudine/zidovudine*:* 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).

Table 2. Effect of Coadministered Drugs on Lamivudine and Zidovudine AUC*

Note: ROUTINE DOSE MODIFICATION OF LAMIVUDINE AND ZIDOVUDINE IS NOT WARRANTED WITH COADMINISTRATION 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 43%	90% CI: 32% to 55%	↔
Drugs That May Alter Zidovudine Blood Concentrations					
Coadministered Drug and Dose	**Zidovudine Dose**	**n**	**Zidovudine Concentrations**		**Concentration of Coadministered Drug**
Atovaquone 750 mg q 12 hr with food	200 mg q 8 hr	14	↑AUC 31%	Range 23% to 78%†	↔

Fluconazole 400 mg daily	200 mg q 8 hr	12	↑ AUC 74%	95% CI: 54% to 98%	Not Reported
Methadone 30 to 90 mg daily	200 mg q 4 hr	9	↑ AUC 43%	Range 16% to 64%†	↔
Nelfinavir 750 mg q 8 hr x 7 to 10 days	single 200 mg	11	↓AUC 35%	Range 28% to 41%	↔
Probenecid 500 mg q 6 hr x 2 days	2 mg/kg q 8 hr x 3 days	3	↑AUC 106%	Range 100% to 170%†	Not Assessed
Ritonavir 300 mg q 6 hr x 4 days	200 mg q 8 hr x 4 days	9	↓AUC 25%	95% CI: 15% to 34%	↔
Valproic acid 250 mg or 500 mg q 8 hr x 4 days	100 mg q 8 hr x 4 days	6	↑ AUC 80%	Range 64% to 130%†	Not Assessed

↑= Increase; ↓= Decrease; ↔= no significant change;

AUC = area under the concentration versus time curve; CI = confidence interval.

*This table is not all inclusive.

†Estimated range of percent difference.

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 patient (see WARNINGS).

Efavirenz:

Drug Interactions (see also CONTRAINDICATIONS and PRECAUTIONS: Drug Interactions)

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. Coadministration of efavirenz with drugs primarily metabolized by 2C9, 2C19, and 3A4 isozymes may result in altered plasma

concentrations of the coadministered 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 coadministered or drugs commonly used as probes for pharmacokinetic interaction. The effects of coadministration of efavirenz on the AUC and C_{max} are summarized in Table 2 (effect of efavirenz on other drugs) and Table 3 (effect of other drugs on efavirenz). For information regarding clinical recommendations see **PRECAUTIONS: Drug Interactions**.

Table 3: Effect of Efavirenz on Coadministered Drug Plasma C_{max}, AUC, and C_{min}

Coadministered 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%)	↔

Table 3: Effect of Efavirenz on Coadministered Drug Plasma C_{max}, AUC, and C_{min}

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Coadministered Drug (mean % change) C_{max} (90% CI)	AUC (90% CI)	C_{min} (90%CI)
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
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 q 12h days 2 -7	300 mg x 7 days		↓36%[i] (21 – 49%)	↓55%[i] (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				↓ 15%	↓ 32%	↓ 48%

Table 3: Effect of Efavirenz on Coadministered Drug Plasma C_{max}, AUC, and C_{min}

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Coadministered Drug (mean % change) C_{max} (90% CI)	AUC (90% CI)	C_{min} (90%CI)
(including metabolites)				(2-26%)	(21-41%)	(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[j]
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%)
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.

Table 3: Effect of Efavirenz on Coadministered Drug Plasma C_{max}, AUC, and C_{min}

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Coadministered Drug (mean % change) C_{max} (90% CI)	AUC (90% CI)	C_{min} (90%CI)

[i] relative to steady-state administration of voriconazole (400 mg for 1 day, then 200 mg po q12h for 2 days).
[j] Not available because of insufficient data.
NA = not available.

Table 4: Effect of Coadministered Drug on Efavirenz Plasma C_{max}, AUC, and C_{min}

Coadministered 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%)
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%)

Table 4: Effect of Coadministered Drug on Efavirenz Plasma C_{max}, AUC, and C_{min}

Coadministered 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)
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
				↓14%[f] (7-21%)	↔[f]	
	300 mg po q12h days 2-7	300 mg x 7 days		↔[f]	↑17%[f] (6-29%)	NA
	400 mg po q12h days 2-7	300 mg x 7 days				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	↔	↔	↔
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.

Table 4: Effect of Coadministered Drug on Efavirenz Plasma C_{max}, AUC, and C_{min}

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Efavirenz (mean % change) C_{max} (90% CI)	AUC (90% CI)	C_{min} (90%CI)

[b] 95% CI.
[c] Soft Gelatin Capsule.
[d] Tenofovir disoproxil fumarate.
[e] 90% CI not available.
[f] Relative to steady-state administration of efavirenz (600 mg once daily for 9 days).
NA = not available.

INDICATIONS AND USAGE

Lamivudine/zidovudine Tablet co-packaged with Efavirenz Tablet is indicated for patients > 12 years of age and those weighing ≥40kg for the treatment of HIV infection**.**

CONTRAINDICATIONS

Lamivudine/zidovudine Tablets co-packaged with efavirenz are contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of the product.

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 (eg, cardiac arrhythmias, prolonged sedation, or respiratory depression). Efavirenz should not be administered concurrently with standard doses of voriconazole because efavirenz significantly decreases voriconazole plasma concentrations (see **DRUG INTERACTIONS, Tables 2 and 3; PRECAUTIONS: Drug Interactions, Table 5).**

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WARNINGS

Lamivudine/Zidovudine Tablets co-packaged with Efavirenz Tablets should not be administered concomitantly with other formulations containing any of these three drugs. The complete prescribing information for all agents being considered for use with the combination of Lamivudine/Zidovudine Tablets co-packaged with Efavirenz Tablets should be consulted before combination therapy with lamivudine/ zidovudine and efavirenz tablets are initiated.

Lamivudine/Zidovudine Tablets:

Bone Marrow Suppression: Lamivudine/zidovudine should be used with caution in patients who have bone marrow suppression evidenced by granulocyte count <1,000 cells/mm^3 or hemoglobin <9.5 g/dL (see ADVERSE REACTIONS). Frequent blood counts are strongly recommended in patients with advanced HIV disease who are treated with lamivudine/zidovudine

Tablets. For HIV-infected individuals and patients with asymptomatic or early HIV disease, periodic blood counts are recommended.

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 lamivudine, zidovudine, and other antiretrovirals. 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 combination of lamivudine and zidovudine to any patient with known risk factors for liver disease; however cases have also been reported in patients with no known risk factors. Treatment with lamivudine/zidovudine 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).

Myopathy*:* Myopathy and myositis with pathological changes, similar to that produced by HIV disease, have been associated with prolonged use of zidovudine, and therefore may occur with therapy with lamivudine/zidovudine tablets.

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 hepatitis B viral DNA (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 posttreatment exacerbations of hepatitis.

Use with Interferon - and Ribavirin-Based Regimens: *In vitro* studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine and zidovudine. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV/HCV virologic suppression) was seen when ribavirin was co-administered with lamivudine/zidovudine tablets in HIV/HCV co-infected patients (see PRECAUTIONS: Drug

Interactions), hepatic decompensation (some fatal) has occurred in HIV/HCV co-infected patients receiving combination antiretroviral therapy for HIV and interferon alfa with or without ribavirin. Patients receiving interferon alfa with or without ribavirin and Lamivudine//Zidovudine should be closely monitored for treatment-associated toxicities, especially hepatic decompensation, neutropenia, and anemia. Discontinuation of lamivudine/zidovudine tablets should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, 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).

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 transciptase 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 this drug is used during the first trimester of pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus.

There are no adequate and well-controlled studies 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 288 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

General

The duration of clinical benefit from antiretroviral therapy may be limited. Patients receiving antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with associated HIV diseases.

Lamivudine/Zidovudine Tablet:

Patients with HIV and Hepatitis B Virus Co-infection: 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. 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**).

Lamivudine/Zidovudine Tablet Co-packaged with Efavirenz:

Fat Redistribution: Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Immune Reconstitution Syndrome: Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including lamivudine, zidovudine and efavirenz. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia (PCP), or tuberculosis), which may necessitate further evaluation and treatment.

The Lamivudine/Zidovudine Tablet Co-packaged with Efavirenz tablets are not recommended for patients with impaired renal function or for patients with impaired hepatic function (see WARNINGS; CLINICAL PHARMACOLOGY, *Pharmacokinetics in Special Populations:* Renal Impairment; DOSAGE AND ADMINISTRATION, Dosage adjustment).

Efavirenz Tablet:

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).

Because of the extensive cytochrome P450-mediated metabolism of efavirenz and limited clinical experience in patients with hepatic impairment, caution should be exercised in administering efavirenz to these patients.

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 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

Lamivudine/zidovudine Tablets and co-packaged with efavirenz Tablets are not a cure for HIV infection and patients may continue to experience illnesses associated with HIV infection, including opportunistic infections and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with HIV-associated diseases.

Patients should be advised of the importance of taking lamivudine/zidovudine Tablets co-packaged with efavirenz tablet on a regular dosing schedule and to avoid missing doses. Patients should be advised that the use of combination of lamivudine, zidovudine, and efavirenz has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

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.

Lamivudine: Patients co-infected with HIV 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.

Zidovudine: Patients should be informed that the major toxicities associated with zidovudine are neutropenia and/or anemia. They should be told of the extreme importance of having their blood counts followed closely while on therapy, especially for patients with advanced HIV disease.

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 Insert (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 medication or herbal products, particularly St. John's wort.

Drug Interactions

Lamivudine/Zidovudine Tablets co-packaged with Efavirenz Tablets should not be prescribed for patients requiring dose adjustments:

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). The effect of higher doses of TMP/SMX on lamivudine pharmacokinetics has not been investigated (see CLINICAL PHARMACOLOGY Table 2). No data are available regarding the potential for 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/zidovudine tablets in combination with zalcitabine is not recommended.

Zidovudine:

See CLINICAL PHARMACOLOGY for information on zidovudine concentrations when co-administered with other drug.

Antiretroviral Agents: Concomitant use of stavudine with lamivudine/zidovudine Tablets should be avoided since an antagonistic relationship between zidovudine and stavudine has been demonstrated *in vitro*. Some nucleoside analogues affecting DNA replication, such as ribavirin, antagonize the *in vitro* antiviral activity of zidovudine against HIV; concomitant use of such drugs should be avoided.

Doxorubicin: Concomitant use of lamivudine/zidovudine Tablets with doxorubicin should be avoided since an antagonistic relationship between zidovudine and doxorubicin has been demonstrated *in vitro.*

Phenytoin*:* Phenytoin plasma levels have been reported to be low in some patients receiving zidovudine while in one case a high level was documented. However, in a pharmacokinetic interaction study in which 12 HIV-positive volunteers received a single 300-mg phenytoin dose alone and during steady-state zidovudine conditions (200 mg every 4 hours), no change in phenytoin kinetics was observed. Although not designed to optimally assess the effect of phenytoin on zidovudine kinetics, a 30% decrease in oral zidovudine clearance was observed with phenytoin.

Use with Interferon- and Ribavirin-Based Regimens: No evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV/HCV virologic suppression) was seen when ribavirin was co-administered with lamivudine or zidovudine. However, HIV/HCV co-infected patients who were administered zidovudine, in combination with pegylated interferon and ribavirin developed severe neutropenia (ANC <500) and severe anemia (hemoglobin <8 g/dL) more frequently than similar patients not receiving zidovudine (neutropenia 15% vs. 9%, anemia 5% vs. 1%).

Overlapping Toxicities: Coadministration of ganciclovir, interferon-α, and other bone marrow suppressive or cytotoxic agents may increase the hematologic toxicity of zidovudine.

Efavirenz:

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. Coadministration of efavirenz with drugs primarily

metabolized by these isozymes may result in altered plasma concentrations of the coadministered drug. Therefore, appropriate dose adjustments may be necessary for these drugs.

Drugs which induce CYP3A4 activity (eg, 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 5 and 6.

Table 5: 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 3 and 4.
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.

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Deleted: CONTRAINDICATED at standard doses. 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. When voriconazole is coadministered with efavirenz, voriconazole maintenance dose should be increased to 400 mg every 12 hours and efavirenz dose should be decreased to 300 mg once daily using the capsule formulation. Efavirenz tablets should not be broken. (See **CLINICAL PHARMACOLOGY**, Tables 3 and 4; **CONTRAINDICATIONS**; and **DOSAGE AND ADMINISTRATION: Dosage Adjustment**.)¶

¶

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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 3 and 4.¶

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Table 6: 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.

Table 6: 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
Anticonvulsants:		
Carbamazepine	↓ carbamazepine[a] ↓ efavirenz[a]	There are insufficient data to make a dose recommendation for efavirenz. Alternative anticonvulsant treatment should be used.
Phenytoin Phenobarbital	↓ anticonvulsant ↓ efavirenz	Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.
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).

Table 6: 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
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]	
Narcotic analgesic: Methadone	↓ methadone[a]	Coadministration 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 3 and 4 for magnitude of established interactions.
[b] This table is not all-inclusive.

Other Drugs: Based on the results of drug interaction studies (see Tables 3 and 4), 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 since 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

Carcinogenicity:

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.

Zidovudine: Zidovudine was administered orally at 3 dosage levels to separate groups of mice and rats (60 females and 60 males in each group). Initial single daily doses were 30, 60, and 120 mg/kg/day in mice and 80, 220, and 600 mg/kg/day in rats. The doses in mice were reduced to 20, 30, and 40 mg/kg/day after day 90 because of treatment-related anemia, whereas in rats only the high dose was reduced to 450 mg/kg/day on day 91 and then to 300 mg/kg/day on day 279.

In mice, 7 late-appearing (after 19 months) vaginal neoplasms (5 non-metastasizing squamous cell carcinomas, 1 squamous cell papilloma, and 1 squamous polyp) occurred in animals given the highest dose. One late-appearing squamous cell papilloma occurred in the vagina of a middle-dose animal. No vaginal tumors were found at the lowest dose.

In rats, 2 late-appearing (after 20 months), non-metastasizing vaginal squamous cell carcinomas occurred in animals given the highest dose. No vaginal tumors occurred at the low or middle dose in rats. No other drug-related tumors were observed in either sex of either species.

At doses that produced tumors in mice and rats, the estimated drug exposure (as measured by AUC) was approximately 3 times (mouse) and 24 times (rat) the estimated human exposure at the recommended therapeutic dose of 100 mg every 4 hours.

Two transplacental carcinogenicity studies were conducted in mice. One study administered zidovudine at doses of 20 mg/kg/day or 40 mg/kg/day from gestation day 10 through parturition and lactation with dosing continuing in offspring for 24 months postnatally. The doses of zidovudine employed in this study produced zidovudine exposures approximately 3 times the estimated human exposure at recommended doses. After 24 months at the highest dose, an increase in incidence of vaginal tumors was noted with no increase in tumors in the liver or lung or any other organ in either gender. These findings are consistent with results of the standard oral carcinogenicity study in mice, as described earlier. A second study administered zidovudine at maximum tolerated doses of 12.5 mg/day or 25 mg/day (~1,000 mg/kg nonpregnant body weight or ~450 mg/kg of term body weight) to pregnant mice from days 12 through 18 of gestation. There was an increase in the number of tumors in the lung, liver, and female reproductive tracts in the offspring of mice receiving the higher dose level of zidovudine.

It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

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.

Mutagenicity:

Lamivudine*:* Lamivudine was mutagenic in an L5178Y/TK+/- mouse lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes. Lamivudine was negative in a microbial mutagenicity assay, in an in vitro cell transformation assay, in a rat micronucleus test, in a rat bone marrow cytogenetic assay, and in an assay for unscheduled DNA synthesis in rat liver.

Zidovudine*:* Zidovudine was mutagenic in an L5178Y/TK+/- mouse lymphoma assay, positive in an *in vitro* cell transformation assay, clastogenic in a cytogenetic assay using cultured human lymphocytes, and positive in mouse and rat micronucleus tests after repeated doses. It was negative in a cytogenetic study in rats given a single dose.

Efavirenz: 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.

Impairment of fertility:

Lamivudine: In a study of reproductive performance, lamivudine, administered to male and female rats at doses up to 130 times the usual adult dose based on body surface area considerations, revealed no evidence of impaired fertility (judged by conception rates) and no effect on the survival, growth, and development to weaning of the offspring.

Zidovudine*:* Zidovudine, administered to male and female rats at doses up to 7 times the usual adult dose based on body surface area considerations, had no effect on fertility judged by conception rates.

Efavirenz: 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:

Lamivudine/Zidovudine Tablet*:*

Pregnancy Category C

There are no adequate and well-controlled studies of the combination product in pregnant women. Reproduction studies with lamivudine and zidovudine have been performed in animals (see lamivudine and zidovudine sections below). Lamivudine/zidovudine Tablets should be used during pregnancy only if the potential benefits outweigh the risks.

Lamivudine:

Reproduction studies with orally administered lamivudine have been performed in rats and rabbits at 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 embryolethality 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 those 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 μg/mL (150 mg twice daily) and 2.1 to 5.2 μg /mL (300 mg twice daily) and were typically greater than 2 times the maternal serum levels (see **ADVERSE REACTIONS**).

Zidovudine: Reproduction studies with orally administered zidovudine in the rat and in the rabbit at doses up to 500 mg/kg/day revealed no evidence of teratogenicity with zidovudine. Zidovudine treatment resulted in embryo/fetal toxicity as evidenced by an increase in the incidence of fetal resorptions in rats given 150 or 450 mg/kg/day and rabbits given 500 mg/kg/day. The doses used in the teratology studies resulted in peak zidovudine plasma concentrations (after one half of the daily dose) in rats 66 to 226 times, and in rabbits 12 to 87 times, mean steady-state peak human plasma concentrations (after one sixth of the daily dose) achieved with the recommended daily dose (100 mg every 4 hours). In an additional teratology study in rats, a dose of 3,000 mg/kg/day (very near the oral median lethal dose in rats of 3,683 mg/kg) caused marked maternal toxicity and an increase in the incidence of fetal malformations. This dose resulted in peak zidovudine plasma concentrations 350 times peak human plasma concentrations. No evidence of teratogenicity was seen in this experiment at doses of 600 mg/kg/day or less. Two rodent carcinogenicity studies were conducted (see Carcinogenesis, Mutagenesis, and Impairment of Fertility).

A randomized, double blind, placebo-controlled trial was conducted in HIV-infected pregnant women to determine the utility of zidovudine for the prevention of maternal-fetal HIV-transmission. Congenital abnormalities occurred with similar frequency between neonates born to mothers who received zidovudine and neonates born to mothers who received placebo. Abnormalities were either problems in embryogenesis (prior to 14 weeks) or were recognized on ultrasound before or immediately after initiation of study drug.

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.

Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving** lamivudine/zidovudine tablets co-packaged with efavirenz.

No specific studies of lamivudine and zidovudine excretion in breast milk after dosing with lamivudine and zidovudine tablets have been performed. Lamivudine and zidovudine are excreted in human breast milk (see **CLINICAL PHARMACOLOGY: Pharmacokinetics: Nursing Mothers**).

A study in lactating rats administered 45 mg/kg of lamivudine showed that lamivudine concentrations in milk were slightly greater than those in plasma. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving lamivudine/zidovudine tablets.

Pediatric Use

Adjustment of the dose of lamivudine/zidovudine tablet co-packaged with efavirenz tablet is not possible with this combination. Therefore, lamivudine/zidovudine tablets co-packaged with efavirenz tablets are not recommended for patients < 12 years of age or those who weigh < 40 kg.

Geriatric Use

Lamivudine/zidovudine co-packaged with efavirenz tablets: Clinical studies of this combination did not include sufficient numbers of subjects aged 65 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 drug therapy. Lamivudine/Zidovudine Tablets co-packaged with efavirenz Tablets are not recommended for patients with impaired renal function or impaired hepatic function. .

ADVERSE REACTIONS

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

Lamivudine/Zidovudine Administered As Separate Formulations: In 4 randomized, controlled trials of lamivudine 300 mg per day plus zidovudine 600 mg per day, the following selected clinical and laboratory adverse events were observed (see Table 7 and Table 8).

Table 7: Selected Clinical Adverse Events (≥5% Frequency) in 4 Controlled Clinical Trials With lamivudine 300 mg/day and zidovudine 600 mg/day

Adverse Event	Lamivudine 150 mg twice daily plus zidovudine (n=251)
Body as a whole	
Headache	35%
Malaise & fatigue	27%
Fever or chills	10%
Digestive	
Nausea	33%
Diarrhea	18%
Nausea & vomiting	13%
Anorexia and/or decreased appetite	10%

Abdominal pain	9%
Abdominal cramps	6%
Dyspepsia	5%
Nervous system	
Neuropathy	12%
Insomnia & other sleep disorders	11%
Dizziness	10%
Depressive disorders	9%
Respiratory	
Nasal signs & symptoms	20%
Cough	18%
Skin	
Skin rashes	9%
Musculoskeletal	
Musculoskeletal pain	12%
Myalgia	8%
Arthralgia	5%

Pancreatitis was observed in 9 of the 2,613 adult patients (< 0.3%) who received lamivudine in the controlled clinical trials.

Selected laboratory abnormalities observed during therapy are listed in Table 8.

Table 8: Frequencies of Selected Laboratory Abnormalities among Adults in 4 Controlled Clinical Trials of Lamivudine 300 mg/day plus Zidovudine 600 mg/day*

Test (Abnormal Level)	**Lamivudine plus Zidovudine % (n)**
Neutropenia (ANC<750/mm^3)	7.2% (237)
Anemia (Hgb<8.0 g/dL)	2.9% (241)
Thrombocytopenia(platelets <50,000/mm^3)	0.4% (240)
ALT (>5.0 x ULN)	3.7% (241)
AST (>5.0 x ULN)	1.7% (241)
Bilirubin (>2.5 x ULN)	0.8% (241)
Amylase (>2.0 x ULN)	4.2% (72)

ULN = Upper limit of normal

ANC = Absolute neutrophil count

n = Number of patients assessed

* Frequencies of these laboratory abnormalities were higher in patients with mild laboratory abnormalities at baseline.

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, zidovudine, and/or combination of lamivudine and zidovudine. 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, zidovudine, and/or combination of lamivudine and zidovudine.

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

Cardiovascular: Cardiomyopathy

Endocrine and Metabolic: Gynecomastia, hyperglycemia.

Gastrointestinal: Oral mucosal pigmentation, stomatitis.

General: Vasculitis, 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, posttreatment exacerbation of hepatitis B. (see WARNINGS).

Hypersensitivity: Sensitization reactions (including anaphylaxis), urticaria.

Musculoskeletal: Muscle weakness, CPK elevation, rhabodmyolysis.

Nervous: Paresthesia, peripheral neuropathy, seizures.

Respiratory: Abnormal breath sounds/wheezing.

Skin: Alopecia, erythema multiforme, Stevens-Johnson syndrome.

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 9 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 11.

Table 9: 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 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 10.

Table 10: 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 discontinuation as a result of rash	—	1.7	8.8	0.3

[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 10, rash is more common in pediatric patients and more often of higher grade (ie, more severe) (see **PRECAUTIONS**).

Experience with efavirenz in patients who discontinued other antiretroviral agents of the NNRTI class is limited. Nineteen patients who discontinued nevirapine because of rash have been treated with efavirenz. Nine of these patients developed mild-to-moderate rash while receiving therapy with efavirenz, and two of these patients discontinued because of rash.

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 11.

Table 11: 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

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, and 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 12.

Table 12: 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)	Efavirenz[a] + Indinavir (n=415)	Indinavir + ZDV/LAM (n=401)	Efavirenz[a] + Nelfinavir + NRTIs (n=64)	Efavirenz[a] + NRTIs (n=65)	Nelfinavir + NRTIs (n=66)
		180 weeks[b]	102 weeks[b]	76 weeks[b]	71.1 weeks[b]	70.9 weeks[b]	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 longterm 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**).

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 since samples were taken from nonfasting patients. The clinical significance of these findings is unknown (see **PRECAUTIONS**).

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

Lamivudine150 mg/Zidovudine 300 mg Tablets co-packaged with efavirenz Tablets: There is no known antidote for lamivudine, zidovudine or efavirenz.

Lamivudine: One case of an adult ingesting 6 grams of lamivudine was reported; there were no clinical signs or symptoms noted and hematologic tests remained normal. 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.

Zidovudine: Acute overdoses of zidovudine have been reported in pediatric patients and adults. These involved exposures up to 50 grams. The only consistent findings were nausea and vomiting. Other reported occurrences included headache, dizziness, drowsiness, lethargy, confusion, and 1 report of a grand mal seizure. Hematologic changes were transient. All patients recovered. Hemodialysis and peritoneal dialysis appear to have a negligible effect on the removal of zidovudine, while elimination of its primary metabolite, GZDV, is enhanced.

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. Since 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 of lamivudine/zidovudine tablet and efavirenz has not been evaluated. Therefore the lamivudine/zidovudine tablet co-packaged with efavirenz should be taken under fasting conditions.

Adults and Adolescents:

The recommended oral dose for adults and adolescents (≥ 12 years of age) who weigh ≥40kg is one Lamivudine/Zidovudine (150mg/300 mg) tablets taken twice daily.

The recommended dosage of efavirenz 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 might 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

Lamivudine/zidovudine tablets co-packaged with efavirenz tablets are not recommended for pediatric patients ≤12 years of age or in pediatric patients weighing <40 kg.

Geriatrics

Although no specific dosage alterations are recommended, caution should be exercised when lamivudine/zidovudine Tablets co-packaged with efavirenz Tablets are administered to geriatric patients (> 65 years of age).

Renal Impairment and hepatic impairment

Lamivudine/zidovudine tablets co-packaged with efavirenz tablets **are** not recommended for patients with renal impairment (creatinine clearance < 50mL/min)or for patients on hemodialysis or with impaired hepatic function.

Monitoring:

Zidovudine: Hematologic toxicities appear to be related to pretreatment bone marrow reserve and to dose and duration of therapy. In patients with poor bone marrow reserve, particularly in patients with advanced symptomatic HIV disease, frequent monitoring of hematologic indices is recommended to detect serious anemia or neutropenia. Dose interruption, dose discontinuation and/or blood transfusion maybe warranted in patients who develop significant anemia. In patients who experience hematologic toxicity, reduction in hemoglobin may occur as early as 2 to 4 weeks, and neutropenia usually occurs after 6 to 8 weeks.

If marrow recovery occurs following dose interruption, resumption in therapy may be appropriate using adjunctive measures such as epoetin alfa at recommended doses, depending on hematologic indices such as serum erythropoietin level and patient tolerance.

For patients experiencing pronounced anemia while receiving chronic coadministration of Lamivudine/Zidovudine Tablets and some other drugs (e.g., fluconazole, valproic acid), dose interruption of Lamivudine/Zidovudine Tablets may be considered.

For patients requiring discontinuation of zidovudine treatment due to hematological toxicity (ies), treatment with lamivudine/zidovudine tablets should be discontinued.

HOW SUPPLIED

Lamivudine/Zidovudine Tablets. Each tablet contain 150 mg lamivudine and 300 mg zidovudine**,** is a white to off white oval shaped film coated tablets with LZ embossed on one side and plain on the other side. 60 tablets are packed in 85ml HDPE container with tear-off cap

Efavirenz Tablets. Each tablet, contain 600 mg of efavirenz, is off white colored, capsule shaped, film-coated tablet, plain on both sides. 30 tablets are packed in 50ml HDPE containers with tear-off cap with EPE (Expanded Polyethylene) Foam filler.

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

Storage:

Lamivudine/zidovudine 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:

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

Manufactured by:

STRIDES ARCOLAB LIMITED,

Bangalore- India

PATIENT PACKAGE INFORMATION

Lamivudine (150 mg)/Zidovudine (300 mg) Tablets Co-Packaged with Efavirenz (600 mg) Tablets

ALERT: Find out about medicines that should NOT be taken with Lamivudine/Zidovudine Tablets Co-Packaged with Efavirenz Tablets. Please also read the section "Who should not take Lamivudine/Zidovudine Tablets Co-Packaged with Efavirenz Tablets".

Carefully read this Patient Package before you start taking the combination of Lamivudine/Zidovudine Tablets co-packaged with Efavirenz Tablets, and each time you get a refill, because there may be new information that is provided. This information does not replace the need to talk with your doctor. You and your doctor should discuss Lamivudine/Zidovudine Tablets co-packaged with Efavirenz Tablets regarding these medicines when you start taking your medicine it and at regular checkups. You should stay under a doctor's care while using these medications. You should consult with your doctor before making any changes to your medications, except in any of the special circumstances described below regarding rash or liver problems.

What important information and other side effects should I know about the lamivudine/zidovudine tablets co-packaged with efavirenz tablets?

Lamivudine/zidovudine tablet can cause

Lactic Acidosis and Liver Problems

Some HIV medicines, including lamivudine/zidovudine tablets can cause a rare but serious condition called lactic acidosis with liver enlargement (hepatomegaly).

Get in touch with your doctor right away if you experience the following symptoms:

- nausea, vomiting, or unusual or unexpected stomach discomfort;
- weakness and tiredness;
- shortness of breath;
- weakness in the arms and legs;
- yellowing of the skin or eyes;
- or pain in the upper stomach area.

These may be early symptoms of lactic acidosis or liver problems. Women (including pregnant women), overweight people, and people who have taken HIV medicines like lamivudine and zidovudine for a long time have a higher chance of developing lactic acidosis and liver enlargement. Lactic acidosis is a medical emergency and must be treated in a hospital. In some cases this condition can cause death

Worsening of hepatitis B virus (HBV) infection

Patients with HBV infection, who take lamivudine/zidovudine tablets and then stop them, may get "flare-ups" of their hepatitis. "Flare-up" is when the disease suddenly returns in a worse way than before. If you have HBV infection, your doctor should closely monitor your liver function for several months after stopping lamivudine/zidovudine tablets. You may need to take anti-HBV medicines.

Hematologic toxicity

Lamivudine/zidovudine tablets have been associated with hematologic toxicity including neutropenia (low count of one of the white cells) and severe anemia, particularly in patients with advanced HIV disease. Prolonged use of lamivudine/zidovudine tablets has been associated with symptomatic myopathy (muscular problems).

Use with interferon- and ribavirin-based regimens

Worsening of liver disease (sometimes resulting in death) has occurred in patients infected with both HIV and hepatitis C infection who are taking anti-HIV medicines and are also being treated for hepatitis C infection with interferon with or without ribavirin. If you are taking Lamivudine/Zidovudine Tablets as well as interferon with or without ribavirin and you experience side effects, be sure to inform your doctor.

Changes in body fat

Changes in body fat develop in some patients taking anti-HIV medicine. These changes may include an increased amount of fat in the upper back and neck ("buffalo hump"), in the breasts, and around the trunk. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these fat changes are not known.

If you experience any of the following serious side effects, stop taking this combination of lamivudine and zidovudine and seek emergency medical attention or notify your doctor immediately:

- an allergic reaction (difficulty breathing; closing of the throat; swelling of the lips, tongue, or face; or hives);
- muscle pain or weakness; or
- peripheral neuropathy (nerve damage), which may cause numbness, tingling, or pain.

Other, less serious side effects may be more likely to occur.

- mild nausea, vomiting, diarrhea, or decreased appetite;
- a headache;
- dizziness;
- depression/anxiety
- myalgia
- fever
- insomnia

Side effects other than those listed here may also occur. Talk to your doctor about any side effect that seems unusual or that is especially bothersome.

Efavirenz can cause

The most significant adverse events observed in patients treated with efavirenz are nervous system symptoms, serious psychiatric symptoms, and skin rash.

Nervous system symptoms: Dizziness, insomnia, impaired concentration, somnolence, abnormal dreaming, euphoria, confusion, agitation, amnesia, hallucinations, stupor, abnormal thinking, and depersonalization.

Serious psychiatric problems: A small number of patients experience severe depression, strange thoughts, or angry behavior while taking efavirenz. Some patients have thoughts of suicide and a few have actually committed suicide. These problems tend to occur more often in patients who have had mental illness. Contact your doctor immediately if you think you are having these psychiatric symptoms, so your doctor can decide if you should continue to take efavirenz.

Changes in body fat

Changes in body fat develop in some patients taking anti-HIV medicine. These changes may include an increased amount of fat in the upper back and neck ("buffalo hump"), in the breasts, and around the trunk. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these fat changes are not known.

Common side effects: Many patients have dizziness, trouble sleeping, drowsiness, trouble concentrating, and/or unusual dreams during treatment with efavirenz. These side effects may be reduced if you take efavirenz at bedtime on an empty stomach. They also tend to go away after you have taken the medicine for a few weeks. If you have these common side effects, such as dizziness, it does not mean that you will also have serious psychiatric problems, such as severe depression, strange thoughts, or angry behavior. Inform your doctor immediately if any of these side effects continue or if they bother you. It is possible that these symptoms may be more severe
if efavirenz is used with alcohol or mood altering (street) drugs.

If you are dizzy, have trouble concentrating, or are drowsy, avoid activities that may be dangerous, such as driving or operating machinery.

Skin rash is common. Rashes usually go away without any change in treatment. In a small number of patients, rash may be serious. If you develop a rash, call your doctor right away. Rash may be a serious problem in some children. Tell your child's doctor right away if you notice rash or any other side effects while your child is on efavirenz treatment.

Other common side effects include tiredness, stomach upset, vomiting, and diarrhea.

Tell your doctor or healthcare provider if you notice any side effects while taking efavirenz.

Contact your doctor before stopping efavirenz because of side effects or for any other reason.

These are not the only side effects possible with use of efavirenz. Ask your doctor or pharmacist for a more complete list of side effects of efavirenz and all the medicines you will take.

What are Lamivudine/Zidovudine Tablets co-packaged with Efavirenz Tablets?

Lamivudine/Zidovudine Tablets are a combination of two drugs, lamivudine and zidovudine. Both Lamivudine and zidovudine are a type of anti-HIV drug called "nucleoside reverse transcriptase inhibitor (NRTI). Efavirenz Tablets is a type of anti-HIV drug called a "non-nucleoside reverse transcriptase inhibitor (NNRTI). These are prescription medications used to treat Human Immunodeficiency Virus type 1 (HIV-1), the virus that causes AIDS (Acquired Immune Deficiency Syndrome). NNRTIs are not used in the treatment of Human Immunodeficiency virus type 2 (HIV-2) infection.

How does Lamivudine/Zidovudine Tablets co-packaged with Efavirenz Tablets work?

When used together, the combination of Lamivudine/Zidovudine Tablets co-packaged with Efavirenz Tablets may help in lowering the amount of HIV in your blood (called "viral load") and increase your CD4 (T) cell count. HIV infection destroys CD4 (T) cells, which are important to the immune system. The immune system helps fight infection. Reducing the amount of HIV and increasing the CD4 (T) cell count may improve your immune system and, may reduce the risk of death or infections that can happen when your immune system is weak..

Does Lamivudine/Zidovudine Tablets co-packaged with Efavirenz Tablets cure HIV or AIDS?

Lamivudine/Zidovudine Tablets co-packaged with Efavirenz Tablets do not cure HIV infection or AIDS. We do not know if Lamivudine/Zidovudine Tablets co-packaged with Efavirenz Tablets will help you live longer or have fewer of the medical problems that people get with HIV or AIDS, such as other infections. Continue to see your doctor regularly and report any medical problems that occur.

Does Lamivudine/Zidovudine Tablets co-packaged with Efavirenz Tablets reduce the risk of passing HIV to others?

Lamivudine/Zidovudine Tablets co-packaged with Efavirenz Tablets do not lower the risk of passing HIV to other people through sexual contact, sharing needles,

or being exposed to your blood. For your health and the health of others, it is important to always practice safe sex by using latex or polyurethane condom or other barrier method to lower the chance of sexual contact with semen, vaginal secretions, or blood. Never re-use or share dirty needles.
Ask you doctor if you have any questions on how to prevent passing HIV to other people.

Who should not take Lamivudine/Zidovudine Tablets Co-Packaged with Efavirenz Tablets?

Together with your doctor, you need to decide whether taking Lamivudine/Zidovudine Tablets co-packaged with Efavirenz Tablets is right for you.

Do not take Lamivudine/Zidovudine Tablets co-packaged with Efavirenz Tablets if you:

- are allergic to any of the ingredients, including the active ingredients lamivudine, ziodovudine and efavirenz, and the inactive ingredients (see **Inactive Ingredients** at the end of this leaflet). Tell your doctor or pharmacist if you think you have had an allergic reaction to any of these ingredients.
- take certain medications (see **Can I take other medicines?** for a list of medicines.) because you could experience serious side effects.
- are less than 12 years or weigh less than 88 pounds (40kg).

Also do not restart these medications after you recover from side effects of these medications such as serious psychiatric problems, lactic acidosis or liver problems, or skin reactions that happened when you took these medications without the advice of your doctor.

What should I tell my doctor before taking these medications?

Before taking the lamivudine/zidovudine tablets co-packaged with efavirenz, tell your doctor if you:

- have kidney disease or are undergoing dialysis;
- have liver disease or have had hepatitis (inflammation of the liver);
- have ever had mental illness or are using drugs or alcohol;
- have skin conditions, such as a rash;
- have ever had seizures or are taking medicine for seizures (for example, phenytoin, carbamazepine, or Phenobarbital). Your doctor may want to check drug levels in your blood from time to time;
- are pregnant, planning to become pregnant, or are breast feeding.

How should I take Lamivudine/Zidovudine Tablets co-packaged with Efavirenz Tablets? How should I store them?

- You should take Lamivudine/Zidovudine Tablets co-packaged with Efavirenz Tablets on an empty stomach, preferably at bedtime.
- Taking Efavirenz Tablets with food increases the amount of medicine in your body, which may increase the frequency of side effects.
- Taking Efavirenz Tablets at bedtime my make some side effects less bothersome.

Adults and Adolescents

The recommended oral dose for adults and adolescents older than 12 years of age who weigh more than or equal to 40 kg (88 pounds) is:

- One Lamivudine/Zidovudine (150 mg/ 300 mg) Tablet taken twice daily. Lamivudine/Zidovudine Tablets should be taken every 12 hours on an empty stomach AND
- one Efavirenz (600 mg) Tablet taken once daily on an empty stomach, at bedtime.

Pediatrics

Lamivudine/Zidovudine Tablets co-packaged with Efavirenz Tablets are not recommended for pediatric patients less than 12 years of age or those who weigh less than 40 kg (88 pounds).

Store Lamivudine/Zidovudine Tablets co-packaged with Efavirenz Tablets at room temperature, between 20° to 25° C (68° to 77° F). Throw away medicines that are no longer needed or out-of-date. Keep all medicines away from children and pets. Do NOT store these medicines in a damp place such as a bathroom medicine cabinet or near the kitchen sink.

What happens if I miss a dose?

Do not miss any doses of Lamivudine/Zidovudine Tablets co-packaged with Efavirenz Tablets. If you forget to take these medications, take them as soon as possible. If it is almost time for the next dose, skip the missed dose and continue your regular dosing schedule. Do not double the next dose.

What should I do if someone has taken an overdose of Lamivudine/Zidovudine Tablets co-packaged with Efavirenz Tablets?

If you suspect that you or someone else has taken an overdose of Lamivudine/Zidovudine Tablets co-packaged with Efavirenz Tablets, get medical help right away. Contact a doctor or a poison control center.

Can I take other medicines with Lamivudine/Zidovudine Tablets co-packaged with Efavirenz Tablets?

Other medications may interact with these medications resulting in decreased effectiveness and/or side effects. Talk to your doctor and pharmacist before taking any other prescription or over-the-counter medicines, including vitamins, minerals, and herbal products including St. John's wort (hypericum perforatum), during treatment. Sometimes serious side effects will happen if your take Lamivudine/Zidovudine Tablets co-packaged with Efavirenz Tablets with certain medicines.

- Do not take Epivir® (Lamivudine, 3TC), Retrovir® (Zidovudine, AZT, ZDV, azidothymidine), Combivir® (lamivudine and zidovudine), Epzicom® (abacavir sulfate and lamivudine), Trizivir® (abacavir sulfate, lamivudine, and zidovudine) or Sustiva® (efavirenz) while taking Lamivudine/Zidovudine Tablets co-packaged with Efavirenz Tablets. Some of these medicines are already in Lamivudine/Zidovudine Tablet co-packaged with Efavirenz tablets.

The following medicines should be avoided when you are taking the combination of Lamivudine/Zidovudine Tablets:

- Trimethoprim (TMP) 160 mg/sulfamethoxazole (SMX) 800 mg can increase the levels of lamivudine in the blood
- Zalcitabine- may interfere with the action of lamivudine.
- Co-administration of ganciclovir, interferon-alpha, and other bone marrow suppressive or anti cancer agents may increase the hematologic toxicity of zidovudine.
- Use of Lamivudine/Zidovudine Tablets along with stavudine should be avoided, since stavudine can interfere with the action of zidovudine. Similarly doxorubicin or ribavirin should be avoided because these medications can also interfere with the action of zidovudine.

Use with interferon- and ribavirin-based regimens. Worsening of liver disease (sometimes resulting in death) has occurred in patients infected with both HIV-1 infection and hepatitis C infection who are taking anti-HIV medicines and are also being treated for hepatitis C with interferon with or without ribavirin. If you are taking Lamivudine/Zidovudine Tablets as well as interferon with or without ribavirin and you experience side effects, be sure to tell your doctor

Efavirenz Tablets:

The following medicines may cause serious and life-threatening side effects when taken with efavirenz. You should **not** take any of these medicines while taking efavirenz:

- Hismanal® (astemizole)
- Vascor® (bepridil)
- Propulsid® (cisapride)
- Versed® (midazolam)
- Orap® (pimozide)
- Halcion® (triazolam)
- Ergot medications (for example, Wigraine® and Cafergot®)

The following medicine should **not** be taken with efavirenz since it may lose its effect or may increase the chance of having side effects from efavirenz:

• Vfend® (voriconazole). Some doses of voriconazole can be taken at the same time with a lower dose of efavirenz, but you must check with your doctor first.

• St. John's wort (Hypericum perforatum)

The following medicines may need to be replaced with another medicine when taken with efavirenz:

- Fortovase®, Invirase® (saquinavir)
- Biaxin® (clarithromycin)
- Carbatrol®, Tegretol® (carbamazepine)
- Sporanox® (itraconazole)

The following medicines may require a change in the dose of either Efavirenz or the other medicine:

- Calcium channel blockers such as Cardizem® or Tiazac® (diltiazem), Covera HS® or Isoptin SR® (verapamil), and others.
- The cholesterol-lowering medicines Lipitor® (atorvastatin), PRAVACHOL® (pravastatin), and Zocor® (simvastatin).
- Crixivan® (indinavir)
- Kaletra® (lopinavir/ritonavir)
- Methadone
- Mycobutin® (rifabutin)
- REYATAZ® (atazanavir sulfate). If you are taking Efavirenz and REYATAZ, you should also be taking Norvir® (ritonavir).
- Rifadin® (rifampin) or the rifampin-containing medicines Rifamate® and Rifater®.
- Zoloft® (sertraline)

These are not all the medicines that may cause problems if you take efavirenz. Be sure to tell your doctor or pharmacist about any other medicines, vitamins, supplements, or herbal preparations you are taking.

What about pregnancy and nursing (breast-feeding)?

- Women taking Lamivudine/Zidovudine Tablets co-packaged with Efavirenz Tablets should not become pregnant. Serious birth defects have been seen in the offspring of animals and women treated with efavirenz during pregnancy. It is not known whether efavirenz caused these defects. **Tell your doctor right away if you are pregnant.** Also talk with your doctor if you want to become pregnant.
- Women should not rely only on hormone-based birth control, such as pills, injections, patches or implants, because Efavirenz Tablets may make these contraceptives ineffective. Women must use a reliable form of barrier contraction, such as a condom or diaphragm, even if they also use other methods of birth control.
- The Centers for Disease Control and Prevention (CDC) recommends that mothers with HIV **not** breast-feed because they can pass the HIV through their milk to the baby. Therefore, do not nurse a baby while taking Lamivudine/Zidovudine Tablets co-packaged with Efavirenz Tablets. Also, efavirenz may pass through breast milk and cause serious harm to the baby. Talk with your doctor if you are breast-feeding. You may need to stop breast-feeding or use a different medicine.

General information

Do not use these medications for a condition for which it was not prescribed. Do not give these medications to other people, even if they have the same condition you have. It may harm them.

This Patient Package Information summarizes the most important information about Lamivudine/Zidovudine Tablets co-packaged with Efavirenz Tablets. If you have questions or concerns, or want more information about Lamivudine/Zidovudine Tablets co-packaged with Efavirenz, your doctor or your pharmacist have the complete prescribing information upon which this leaflet was based. You may want to read it and discuss it with your doctor or other healthcare professional. Remember, no written summary can replace careful discussion with your doctor.

What are the ingredients in Lamivudine/Zidovudine Tablets co-packaged with Efavirenz Tablets?

Active ingredients: lamivudine, zidovudine and efavirenz.

Inactive ingredients:

Lamivudine/zidovudine tablets: The inactive ingredients in the lamivudine/zidovudine tablet includes microcrystalline cellulose, sodium starch glycolate, povidone, colloidal silicon dioxide, talc, magnesium stearate, color Opadry white(Y-1-7000), purified water and isopropyl alcohol. Opadry white contains Hydroxy Propyl methylcellulose 2910/ Hypromellose 5cP, Titanium dioxide, Polyethylene glycol 400 (Macrogol).

Efavirenz Tablets: The inactive ingredients in the efavirenz tablet include 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.

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