

## Lamivudine, Stavudine and Efavirenz tablets

### Lamivir - SE Kit

**WARNING: RISK OF LACTIC ACIDOSIS, EXACERBATIONS OF HEPATITIS B IN CO-INFECTED PATIENTS UPON DISCONTINUATION OF LAMIVUDINE**

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 AND STAVUDINE (SEE WARNINGS AND PRECAUTIONS). SUSPEND TREATMENT IF CLINICAL OR LABORATORY FINDINGS SUGGESTIVE OF LACTIC ACIDOSIS OR PRONOUNCED HEPATOTOXICITY OCCUR (SEE WARNINGS AND PRECAUTIONS). FATAL LACTIC ACIDOSIS HAS BEEN REPORTED IN PREGNANT WOMEN WHO RECEIVED THE COMBINATION OF STAVUDINE AND DIDANOSINE WITH OTHER ANTIRETROVIRAL AGENTS. THE COMBINATION OF STAVUDINE AND DIDANOSINE SHOULD BE USED WITH CAUTION DURING PREGNANCY AND IS RECOMMENDED ONLY IF THE POTENTIAL BENEFIT CLEARLY OUTWEIGHS THE POTENTIAL RISK (SEE WARNINGS AND PRECAUTIONS: PREGNANCY).

FATAL AND NON-FATAL PANCREATITIS HAVE OCCURRED DURING THERAPY WHEN STAVUDINE WAS PART OF A COMBINATION REGIMEN THAT INCLUDED DIDANOSINE IN BOTH TREATMENT-NAIVE AND TREATMENT-EXPERIENCED PATIENTS, REGARDLESS OF THE DEGREE OF IMMUNOSUPPRESSION (SEE WARNINGS AND PRECAUTIONS).

SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO ARE CO-INFECTED WITH HEPATITIS B VIRUS (HBV) AND HUMAN IMMUNODEFICIENCY VIRUS (HIV-1) AND HAVE DISCONTINUED LAMIVUDINE, WHICH IS ONE OF THE COMPONENTS OF THE KIT. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE LAMIVIR-SE KIT AND ARE COINFECTED WITH HIV-1 AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS AND PRECAUTIONS).

## COMPOSITION

### LAMIVIR-SE 30 KIT

Each kit contains

(A) One efavirenz tablet

Each film-coated tablet contains  
Efavirenz.... 600 mg

(B)Two lamivudine and stavudine fixed-dose combination tablets

Each film-coated tablet contains  
Lamivudine....150 mg and  
Stavudine....30 mg

## DOSAGE FORM

**Lamivir-S:** Fixed-dose combination oral tablet  
**Efavir** : Film-coated oral tablet

## DESCRIPTION

Each **Lamivir-SE Kit** contains 3 tablets – 2 fixed dose combination tablets of lamivudine and stavudine and 1 tablet of efavirenz.

Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. It is a non-competitive inhibitor of HIV-1 reverse transcriptase and does not significantly inhibit HIV-2 reverse transcriptase or cellular DNA polymerases alpha, beta, gamma or delta.

Both stavudine and lamivudine belong to the nucleoside analogue class of antiretroviral drugs. Both drugs act by terminating the growth of the DNA chain and inhibiting the reverse transcriptase of HIV.

## PHARMACOLOGY

### Pharmacodynamics

**Lamivudine:** 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 reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue into viral DNA. 3TC-TP is a weak inhibitor of mammalian DNA polymerases  $\alpha$ ,  $\beta$  and  $\gamma$ .

**Stavudine:** Stavudine, a nucleoside analogue of thymidine, is phosphorylated by cellular kinases to the active metabolite, stavudine triphosphate. Stavudine triphosphate inhibits the activity of HIV-1 reverse transcriptase (RT) by competing with the natural substrate thymidine triphosphate ( $K_i=0.0083$  to  $0.032 \mu\text{M}$ ) and by causing DNA chain termination following its incorporation into viral DNA. Stavudine triphosphate inhibits cellular DNA polymerases  $\beta$  and  $\gamma$  and markedly reduces the synthesis of mitochondrial DNA.

**Efavirenz:** Efavirenz (EFV) is an NNRTI of HIV-1. EFV activity is mediated predominantly by noncompetitive inhibition of HIV-1 reverse transcriptase (RT). HIV-2 RT and human cellular DNA polymerases  $\alpha$ ,  $\beta$ ,  $\gamma$  and  $\delta$  are not inhibited by EFV.

## Pharmacokinetics

### *Lamivudine*

The pharmacokinetic properties of lamivudine have been studied in asymptomatic, HIV-1 infected-adult patients after administration of single intravenous (I.V.) doses ranging from 0.25 to 8 mg/kg, as well as single and multiple (twice-daily regimen) oral doses ranging from 0.25 to 10 mg/kg.

The pharmacokinetic properties of lamivudine have also been studied as single and multiple oral doses ranging from 5mg to 600 mg/day, administered to HBV -infected patients. The steady-state pharmacokinetic properties of the lamivudine 300 mg tablet once daily for 7 days compared with the lamivudine 150-mg tablet twice daily for 7 days were assessed in a crossover study in 60 healthy volunteers. Lamivudine 300 mg once daily resulted in lamivudine exposures that were similar to lamivudine 150 mg twice daily with respect to plasma  $AUC_{24,ss}$ ; however,  $C_{max,ss}$  was 66% higher and the trough value was 53% lower compared with the 150 mg twice-daily regimen. Intracellular lamivudine triphosphate exposures in peripheral blood mononuclear cells were also similar with respect to  $AUC_{24,ss}$  and  $C_{max,24,ss}$ ; however, trough values were lower compared with the 150 mg twice-daily regimen. Inter-subject variability was greater for intracellular lamivudine triphosphate concentrations versus lamivudine plasma trough concentrations. The clinical significance of observed differences for both plasma lamivudine concentrations and intracellular lamivudine triphosphate concentrations is not known.

**Absorption and Bioavailability:** Lamivudine was rapidly absorbed after oral administration in HIV-1 infected patients. Absolute bioavailability in 12 adult patients was  $86\% \pm 16\%$  (mean  $\pm$  SD) for the 150-mg tablet and  $87\% \pm 13\%$  for the oral solution. After oral administration of 2 mg/kg twice a day to 9 adults with HIV-1, the peak serum lamivudine concentration ( $C_{max}$ ) was  $1.5 \pm 0.5$  mcg/mL (mean  $\pm$  SD). The area under the plasma concentration versus time curve (AUC) and  $C_{max}$  increased in proportion to the oral dose over the range from 0.25 to 10 mg/kg.

The accumulation ratio of lamivudine in HIV-1-positive asymptomatic adults with normal renal function was 1.50 following 15 days of oral administration of 2 mg/kg twice daily.

### Effects of Food on Oral Absorption

An investigational 25-mg dosage form of lamivudine was administered orally to 12 asymptomatic, HIV-1-infected patients on 2 occasions, once in the fasted state and once with food (1099 kcal; 75 grams fat, 34 grams protein, 72 grams carbohydrate). Absorption of lamivudine was slower in the fed state ( $T_{max}$ :  $3.2 \pm 1.3$  hours) compared with the fasted state ( $T_{max}$ :  $0.9 \pm 0.3$  hours);  $C_{max}$  in the fed state was  $40\% \pm 23\%$  (mean

± SD) lower than in the fasted state. There was no significant difference in systemic exposure ( $AUC_{\infty}$ ) in the fed and fasted states; therefore, lamivudine tablets and oral solution may be administered with or without food.

**Distribution:** The apparent volume of distribution after I.V. administration of lamivudine to 20 patients was  $1.3 \pm 0.4$  L/kg, suggesting that lamivudine distributes into extravascular spaces. Volume of distribution was independent of dose and did not correlate with body weight.

Binding of lamivudine to human plasma proteins is low (<36%). *In vitro* studies showed that over the concentration range of 0.1 to 100 mcg/mL, the amount of lamivudine associated with erythrocytes ranged from 53% to 57% and was independent of concentration.

**Metabolism:** Metabolism of lamivudine is a minor route of elimination. In man, the only known metabolite of lamivudine is the trans-sulfoxide metabolite. Within 12 hours after a single oral dose of lamivudine in 6 HIV-1-infected adults,  $5.2\% \pm 1.4\%$  (mean ± SD) of the dose was excreted as the trans-sulfoxide metabolite in the urine. Serum concentrations of this metabolite have not been determined.

**Elimination:** The majority of lamivudine is eliminated unchanged in urine by active organic cationic secretion. In 9 healthy subjects given a single 300 mg oral dose of lamivudine, renal clearance was  $199.7 \pm 56.9$  mL/min (mean ± SD). In 20 HIV-1-infected patients given a single IV dose, renal clearance was  $280.4 \pm 75.2$  ml/min (mean ± SD), representing  $71\% \pm 16\%$  (mean ± SD) of total clearance of lamivudine. In most single-dose studies in HIV-1-infected patients, HBV-infected patients, or healthy subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life ( $t_{1/2}$ ) ranged from 5 to 7 hours. In HIV-1-infected patients, total clearance was  $398.5 \pm 69.1$  mL/min (mean ± SD). Oral clearance and elimination half-life were independent of dose and body weight over an oral dosing range of 0.25 to 10 mg/kg.

### **Stavudine**

The pharmacokinetics of stavudine has been evaluated in HIV-infected adult and pediatric patients (Tables 1-3). Peak plasma concentrations ( $C_{max}$ ) and area under the plasma concentration-time curve (AUC) increased in proportion to dose after both single and multiple doses ranging from 0.03 to 4 mg/kg. There was no significant accumulation of stavudine with repeated administration every 6, 8, or 12 hours.

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

### **Table 1: Steady-State Pharmacokinetics Parameters of Stavudine in HIV-Infected Adults**

Parameter	Stavudine 40 mg b.i.d. Mean + SD (n=8)
AUC (ng•h/mL) <sup>a</sup>	2568 ± 454
C <sub>max</sub> (ng/mL)	536 ± 146
C <sub>min</sub> (ng/mL)	8 ± 9

<sup>a</sup>from 0 to 24 hours

AUC = area under the curve over 24 hours

C<sub>max</sub> = maximum plasma concentration

C<sub>min</sub> = trough or minimum plasma concentration

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

**Metabolism:** Metabolism plays a limited role in the clearance of stavudine. Unchanged stavudine was the major drug-related component circulating in plasma after an 80-mg dose of <sup>14</sup>C-stavudine, while metabolites constituted minor components of the circulating radioactivity. Minor metabolites include oxidized stavudine, glucuronide conjugates of stavudine and its oxidized metabolite, and an *N*-acetylcysteine conjugate of the ribose after glycosidic cleavage, suggesting that thymine is also a metabolite of stavudine.

**Elimination:** Following an 80-mg dose of <sup>14</sup>C-stavudine to healthy subjects, approximately 95% and 3% of the total radioactivity was recovered in urine and feces, respectively. Radioactivity due to parent drug in urine and feces was 73.7% and 62.0%, respectively. The mean terminal elimination half-life is approximately 2.3 hours following single oral doses. Mean renal clearance of the parent compound is approximately 272 mL/min, accounting for approximately 67% of the apparent oral clearance.

In HIV-infected patients, renal elimination of unchanged drug accounts for about 40% of the overall clearance regardless of the route of administration (Table 2). The mean renal clearance was about twice the average endogenous creatinine clearance, indicating active tubular secretion in addition to glomerular filtration.

**Table 2: Pharmacokinetic Parameters of Stavudine in HIV-Infected Adults: Bioavailability, Distribution and Clearance**

Parameter	Mean ± SD	n
Oral bioavailability (%)	86.4 ± 18.2	25

Volume of distribution (L) <sup>a</sup>	46 ± 21	44
Total body clearance (mL/min) <sup>a</sup>	594 ± 164	44
Apparent oral clearance (mL/min) <sup>b</sup>	560 ± 182 <sup>c</sup>	113
Renal clearance (mL/min) <sup>a</sup>	237 ± 98	39
Elimination half-life, I.V. dose (h) <sup>a</sup>	1.15 ± 0.35	44
Elimination half-life, oral dose (h) <sup>b</sup>	1.6 ± 0.23	8
Urinary recovery of stavudine (% of dose) <sup>a,d</sup>	42 ± 14	39

<sup>a</sup>following 1-hour I.V. infusion

<sup>b</sup>following single oral dose

<sup>c</sup>assuming a body weight of 70 kg

<sup>d</sup> over 12–24 hours

### ***Efavirenz***

***Absorption:*** Peak efavirenz plasma concentrations of 1.6–9.1 µM were attained by 5 hours following single oral doses of 100 mg to 1600 mg administered to uninfected volunteers. Dose-related increases in C<sub>max</sub> and AUC were seen for doses up to 1600 mg; the increases were less than proportional, suggesting diminished absorption at higher doses.

In HIV-1-infected patients at steady state, mean C<sub>max</sub>, mean C<sub>min</sub>, 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<sub>max</sub> was 12.9 ± 3.7 µM (mean ± SD), steady-state C<sub>min</sub> was 5.6 ± 3.2 µM, and the AUC was 184 ± 73 µM•h.

### ***Effect of Food on Oral Absorption***

***Capsules:*** Administration of a single 600 mg dose of efavirenz capsules with a high-fat/high-caloric meal (894 kcal, 54 g fat, 54% calories from fat) or a reduced-fat/normal-caloric meal (440 kcal, 2 g fat, 4% calories from fat) was associated with a mean increase of 22% and 17% in efavirenz AUC<sub>∞</sub> and a mean increase of 39% and 51% in

efavirenz  $C_{max}$ , respectively, relative to the exposures achieved when given under fasted conditions. (see **DOSAGE AND ADMINISTRATION**)

**Tablets:** Administration of a single 600 mg efavirenz tablet with a high-fat/high-caloric meal (approximately 1000 kcal, 500–600 kcal from fat) was associated with a 28% increase in mean  $AUC_{\infty}$  of efavirenz and a 79% increase in mean  $C_{max}$  of efavirenz relative to the exposures achieved under fasted conditions (see **DOSAGE AND ADMINISTRATION**).

**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 1 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 CYP450 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 CYP3A and CYP2B6 are the major isozymes responsible for efavirenz metabolism.

Efavirenz has been shown to induce CYP 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 the feces.

## **INDICATIONS**

**LAMIVIR-SE KIT** is indicated for the treatment of HIV infection in adults.

## **DOSAGE AND ADMINISTRATION**

### **Adult**

#### **Morning**

One white **LAMIVIR-S** tablet (Stavudine 30 mg and lamivudine 150 mg) to be taken in the morning.

### ***Evening***

One white **LAMIVIR-S** tablet (Stavudine 30 mg and lamivudine 150 mg) and one yellow tablet (efavirenz 600 mg) to be taken in the evening. It is recommended that the yellow tablet (efavirenz) be taken on an empty stomach, preferably at bedtime. Bedtime dosing improves the tolerability of nervous system side effects (see **UNDESIRABLE EFFECTS**).

**Dose adjustment :** **LAMIVIR-SE 30/ KIT** should not be prescribed for patients requiring dosage adjustment, such as those with reduced renal function (creatinine clearance  $\leq$  50 ml/min), or those experiencing dose-limiting adverse events.

### **CONTRAINDICATIONS**

**LAMIVIR-SE 30 KIT** is contraindicated in patients with previously demonstrated clinically significant hypersensitivity (eg, anaphylaxis) to any of the components of the product.

#### **Efavirenz**

##### **Hypersensitivity**

Efavirenz is contraindicated in patients with previously demonstrated clinically significant hypersensitivity (eg, Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the components of this product.

##### **Contraindicated Drugs**

For some drugs, competition for CYP3A by efavirenz could result in inhibition of their metabolism and create the potential for serious and/or life-threatening adverse reactions (eg, cardiac arrhythmias, prolonged sedation, or respiratory depression). Drugs that are contraindicated with efavirenz are listed in Table 3.

### **Table 3: Drugs That Are Contraindicated or Not Recommended for Use with Efavirenz**

Drug Class: Drug Name	Clinical Comment
Antimigraine: ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine)	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	Potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.
Calcium channel blocker: bepridil	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
GI motility agent: cisapride	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Neuroleptic: pimozide	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
St. John's wort ( <i>Hypericum perforatum</i> )	May lead to loss of virologic response and possible resistance to efavirenz or to the class of non-nucleoside reverse transcriptase inhibitors (NNRTI).

## WARNINGS AND PRECAUTIONS

### Drug Interactions

#### *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 (eg, trimethoprim). No data are available regarding interactions with other drugs that have renal clearance mechanisms similar to that of lamivudine.

#### **Interferon- and Ribavirin-Based Regimens**

Although no evidence of a pharmacokinetic or pharmacodynamic interaction (eg, loss of HIV-1/HCV virologic suppression) was seen when ribavirin was co-administered with lamivudine in HIV/HCV co-infected patients, 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 (see **WARNINGS AND PRECAUTIONS**).

#### **Zalcitabine**

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

#### **Trimethoprim/Sulfamethoxazole (TMP/SMX)**

No change in the dose of either drug is recommended. There is no information regarding the effect on lamivudine pharmacokinetics of higher doses of TMP/SMX such as those used to treat PCP.

### **Drugs with No Observed Interactions with Lamivudine**

A drug interaction study showed no clinically significant interaction between lamivudine and zidovudine.

### **Stavudine**

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

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

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

Stavudine does not inhibit the major cytochrome P450 isoforms, CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4; therefore, it is unlikely that clinically significant drug interactions will occur with drugs metabolized through these pathways. Because stavudine is not protein-bound, it is not expected to affect the pharmacokinetics of protein-bound drugs.

Tables 4 and 5 summarize the effects on AUC and  $C_{max}$ , with a 95% confidence interval (CI) when available, following co-administration of stavudine with didanosine, lamivudine and nelfinavir. No clinically significant pharmacokinetic interactions were observed.

### **Table 4: Results of Drug Interaction Studies with Stavudine: Effects of Co-administered Drug on Stavudine Plasma AUC and $C_{max}$ Values**

Drug	Stavudine Dosage	n <sup>a</sup>	AUC of Stavudine (95% CI)	C <sub>max</sub> of Stavudine (95% CI)
Didanosine, 100 mg q12h for 4 days	40 mg q12h for 4 days	10	↔	↑ 17%
Lamivudine, 150 mg single dose	40 mg single dose	18	↔ (92.7-100.6%)	↑ 12% (100.3-126.1%)
Nelfinavir, 750 mg q8h for 56 days	30-40 mg q12h for 56 days	8	↔	↔

↑ indicates increase.

↔ indicates no change, or mean increase or decrease of <10%.

<sup>a</sup> HIV-infected patients.

**Table 5: Results of Drug Interaction Studies with Stavudine: Effects of Stavudine on Coadministered Drug Plasma AUC and C<sub>max</sub> Values**

Drug	Stavudine Dosage	n <sup>a</sup>	AUC of Coadministered Drug (95% CI)	C <sub>max</sub> of Coadministered Drug (95% CI)
Didanosine, 100 mg q12h for 4 days	40 mg q12h for 4 days	10	↔	↔
Lamivudine, 150 mg single dose	40 mg single dose	18	↔ (90.5-107.6%)	↔ (87.1-110.6%)
Nelfinavir, 750 mg q8h for 56 days	30-40 mg q12h for 56 days	8	↔	↔

↔ indicates no change, or mean increase or decrease of <10%.

<sup>a</sup> HIV-infected patients.

## **Efavirenz**

Efavirenz plasma concentrations may be altered by substrates, inhibitors, or inducers of CYP3A. Likewise, efavirenz may alter plasma concentrations of drugs metabolized by CYP3A (see **CONTRAINDICATIONS and DRUG INTERACTIONS**).

Efavirenz has been shown *in vivo* to induce CYP3A4. Other compounds that are substrates of CYP3A4 may have decreased plasma concentrations when co-administered with efavirenz. *In vitro* studies have demonstrated that efavirenz inhibits CYP2C9, 2C19, and 3A4 isozymes in the range of observed efavirenz plasma concentrations. Co-administration of efavirenz with drugs primarily metabolized by these isozymes may result in altered plasma concentrations of the co-administered drug. Therefore, appropriate dose adjustments may be necessary for these drugs.

Drugs that 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 Tables 6, 7 and 8.

**Table 6: Established<sup>a</sup> and Other Potentially Significant<sup>b</sup> 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
<b><i>Antiretroviral Agents</i></b>		
Protease inhibitor: Fosamprenavir calcium	↓ Amprenavir	<p><i>Fosamprenavir (unboosted):</i> Appropriate doses of the combinations with respect to safety and efficacy have not been established.</p> <p><i>Fosamprenavir/ritonavir:</i> 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.</p>
Protease inhibitor: Atazanavir	↓ Atazanavir <sup>a</sup>	<p><i>Treatment naïve patients:</i> When co-administered with efavirenz, the recommended dose of atazanavir is 400 mg with ritonavir 100 mg (together once daily with food) and efavirenz 600 mg (once daily on an empty stomach, preferably at bedtime).</p> <p><i>Treatment-experienced patients:</i> Coadministration of efavirenz and atazanavir</p>

		is not recommended.
Protease inhibitor: Indinavir	↓ Indinavir <sup>a</sup>	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 <sub>min</sub> 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 <sup>a</sup>	Lopinavir/ritonavir tablets should not be administered once daily in combination with efavirenz. In antiretroviral-naïve patients, lopinavir/ritonavir tablets can be used twice daily in combination with efavirenz with no dose adjustment. A dose increase of lopinavir/ritonavir tablets to 600/150mg (3 tablets) twice daily may be considered when used in combination with efavirenz in treatment-experienced patients where decreased susceptibility to lopinavir

		is clinically suspected (by treatment history or laboratory evidence). A dose increase of lopinavir/ritonavir oral solution to 533/133 mg (6.5 mL) twice daily taken with food is recommended when used in combination with efavirenz.
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Protease inhibitor: Ritonavir	<p>↑ Ritonavir <sup>a</sup></p> <p>↑ Efavirenz <sup>a</sup></p>	When ritonavir 500 mg q12h was co-administered 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 <sup>a</sup>	Should not be used as sole protease inhibitor in combination with efavirenz.
CCR5 co-receptor antagonist : Maraviroc	↓ Maraviroc <sup>a</sup>	Refer to the full prescribing information for maraviroc for guidance on coadministration with efavirenz.
<b>Other Agents</b>		
Anticoagulant: Warfarin	↑ or ↓ Warfarin	Plasma concentrations and effects potentially increased or decreased by efavirenz.

<p>Anticonvulsants:</p> <p>Carbamazepine</p> <p>Phenytoin Phenobarbital</p>	<p>↓ Carbamazepine<sup>a</sup> ↓ Efavirenz<sup>a</sup></p> <p>↓ Anticonvulsant ↓ Efavirenz</p>	<p>There are insufficient data to make a dose recommendation for efavirenz. Alternative anticonvulsant treatment should be used.</p> <p>Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.</p>
<p>Antidepressant: Sertraline</p>	<p>↓ Sertraline<sup>a</sup></p>	<p>Increases in sertraline dose should be guided by clinical response.</p>
<p>Antifungals:</p> <p>Voriconazole</p>	<p>↓ Voriconazole<sup>a</sup> ↑ efavirenz<sup>a</sup></p>	<p>Efavirenz and voriconazole must not be coadministered 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</p>

<p>Itraconazole</p> <p>Ketoconazole</p> <p>Posaconazole</p>	<p>↓ Itraconazole <sup>a</sup> ↓ Hydroxyitraconazole <sup>a</sup></p> <p>↓ Ketoconazole</p> <p>↓ posaconazole<sup>a</sup></p>	<p>daily using the capsule formulation. Efavirenz tablet should not be broken.</p> <p>Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered.</p> <p>Drug interaction studies with efavirenz and ketoconazole have not been conducted. Efavirenz has the potential to decrease plasma concentrations of ketoconazole.</p> <p>Avoid concomitant use unless the benefit outweighs the risks.</p>
<p>Anti-infective: Clarithromycin</p>	<p>↓ Clarithromycin <sup>a</sup> ↑ 14-OH metabolite <sup>a</sup></p>	<p>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 <b>Other Drug following table</b>). Other macrolide antibiotics, such as erythromycin, have not</p>

		been studied in combination with efavirenz.
Antimycobacterial Rifampin	↓ Efavirenz <sup>a</sup>	Clinical significance of reduced efavirenz concentrations is unknown. Dosing recommendations for concomitant use of efavirenz and rifampin have not been established.
Rifabutin	↓ Rifabutin <sup>a</sup>	Increase daily dose of rifabutin by 50%. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week
Calcium channel blockers: Diltiazem	↓ Diltiazem <sup>a</sup> ↓ Desacetyl diltiazem <sup>a</sup> ↓ N-monodesmethyl diltiazem <sup>a</sup>	Diltiazem dose adjustments should be guided by clinical response (refer to the full prescribing information for diltiazem). No dose adjustment of efavirenz is necessary when administered with diltiazem.
Others (eg, felodipine, nicardipine, nifedipine, verapamil)	↓ Calcium channel blocker	No data are available on the potential interactions of efavirenz with other calcium channel blockers that are substrates of the CYP3A4 enzyme. The potential exists for reduction in plasma concentrations of the calcium channel blocker. Dose adjustments should be guided by clinical response (refer to the complete prescribing information for the calcium channel

		blocker).
HMG-CoA reductase inhibitors: Atorvastatin Pravastatin. Simvastatin	↓ Atorvastatin ↓ Pravastatin ↓ Simvastatin	Plasma concentrations of atorvastatin, pravastatin and simvastatin decreased. Consult the full prescribing information for the HMG-CoA reductase inhibitor for guidance on individualizing the dose.
Hormonal Contraceptives: Oral Ethinyl estradiol / Norgsetimate	↑ active metabolites of norgestimate <sup>a</sup>	A reliable method of barrier contraception must be used in addition to hormonal contraceptives. Efavirenz had no effect on ethinyl estradiol concentrations, but progestin levels (norelgestromin and levonorgestrel) were markedly decreased. No effect of ethinyl estradiol/ norgestimate on efavirenz plasma concentrations was observed.
Implant Etonogestrel	↓ etonogestrel	A reliable method of barrier contraception must be used in addition to hormonal contraceptives. The interaction between etonogestrel and efavirenz has not been studied. Decreased exposure of etonogestrel may be expected. There have been postmarketing reports of contraceptive failure with etonogestrel in efavirenz-exposed patients.
Immunosuppressants:	↓ Immunosuppressant	Decreased exposure of the immunosuppressant may be expected due to CYP3A

Cyclosporine, tacrolimus, sirolimus and others metabolized by CYP3A		induction. These immunosuppressants are not anticipated to affect exposure of efavirenz. Dose adjustments of the immunosuppressant may be required. Close monitoring of immunosuppressant concentrations for at least 2 weeks (until stable concentrations are reached) is recommended when starting or stopping treatment with efavirenz.
Narcotic analgesic: Methadone	↓ Methadone <sup>a</sup>	Co-administration in HIV-infected individuals with a history of injection drug use resulted in decreased plasma levels of methadone and signs of opiate withdrawal. Methadone dose was increased by a mean of 22% to alleviate withdrawal symptoms. Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.

<sup>a</sup> See Tables 7 and 8 for magnitude of established interactions.

<sup>b</sup> This table is not all-inclusive.

### Other Drugs

Based on the results of drug interaction studies, 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.

### **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.

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

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	(mean % change)		
				C <sub>max</sub> (90% CI)	AUC (90% CI)	C <sub>min</sub> (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% <sup>a</sup> (↓ 17-↑ 58%)	↑ 39% <sup>a</sup> (2-88%)	↑ 48% <sup>a</sup> (24-76%)
	300 mg qd/ritonavir 100 mg qd d 1-10 (pm), then 400 mg qd/ritonavir 100 mg qd d 11-24 (pm) (simultaneous with efavirenz)	600 mg qd with a light snack d 11-24 (pm)	14	↑ 17% (8-27%)	↔	↓ 42% (31-51%)
Indinavir	1000 mg q8h x 10 days	600 mg qd x 10 days	20			
	After morning dose			↔ <sup>b</sup>	↓ 33% <sup>b</sup> (26-39%)	↓ 39% <sup>b</sup> (24-51%)
	After afternoon dose			↔ <sup>b</sup>	↓ 37% <sup>b</sup> (26-46%)	↓ 52% <sup>b</sup> (47-57%)
	After evening dose			↓ 29% <sup>b</sup> (11-43%)	↓ 46% <sup>b</sup> (37-54%)	↓ 57% <sup>b</sup> (50-63%)
Lopinavir/ ritonavir	400/100 mg capsule q12h x 9 days	600 mg qd x 9 days	11,7 <sup>c</sup>	↔ <sup>d</sup>	↓ 19% <sup>d</sup> (↓ 36-↑ 3%)	↓ 39% <sup>d</sup> (3-62%)
	600/150 mg tablet q12h x 10 days with efavirenz compared to 400/100 mg q12h alone	600 mg qd x 9 days	23	↑ 36% <sup>d</sup> (28-44%)	↑ 36% <sup>d</sup> (28-44%)	↑ 32% <sup>d</sup> (21-44%)
Nelfinavir	750 mg q8h x 7 days	600 mg qd x 7 days	10	↑ 21% (10-33%)	↑ 20% (8-34%)	↔
Metabolite AG-1402				↓ 40% (30-48%)	↓ 37% (25-48%)	↓ 43% (21-59%)

Ritonavir	500 mg q12h x 8 days	600 mg qd x 10 days	11			
	After AM dose			↑ 24% (12-38%)	↑ 18% (6-33%)	↑ 42% (9-86%) <sup>e</sup>
	After PM dose			↔	↔	↑ 24% (3-50%) <sup>e</sup>
Saquinavir f SGC	1200 mg q8h x 10 days	600 mg qd x 10 days	12	↓ 50% (28-66%)	↓ 62% (45-74%)	↓ 56% (16-77%) <sup>e</sup>
Lamivudine	150 mg q12h x 14 days	600 mg qd x 14 days	9	↔	↔	↑ 265% (37-873%)
Tenofovir g	300 mg qd	600 mg qd x 14 days	29	↔	↔	↔
Zidovudine	300 mg q12h x 14 days	600 mg qd x 14 days	9	↔	↔	↑ 225% (43-640%)
Maraviroc	100 mg bid	600 mg qd	12	↓ 51% (37-62%)	↓ 45% (38-51%)	↓ 45% (28-57%)
Azithromycin	600 mg single dose	400 mg qd x 7 days	14	↑ 22% (4-42%)	↔	NA
Clarithromycin	500 mg q12h x 7 days	400 mg qd 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 qd x 7 days	10	↔	↔	↔
Itraconazole	200 mg q12h x 28 days	600 mg qd x 14 days	18	↓ 37% (20-51%)	↓ 39% (21-53%)	↓ 44% (27-58%)
Hydroxy- itraconazole				↓ 35% (12-52%)	↓ 37% (14-55%)	↓ 43% (18-60%)
Posaconazole	400 mg (oral suspension) bid x 10 and 20 days	400 mg qd x 10 and 20 days	11	↓ 45% (34-53%)	↓ 50% (40-57%)	NA
Rifabutin	300 mg qd x 14 days	600 mg qd 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 qd x 9 days	NA	↓ 61% <sup>h</sup>	↓ 77% <sup>h</sup>	NA
	300 mg po q12h days 2-7	300 mg qd x 7 days	NA	↓ 36% <sup>i</sup> (21-49%)	↓ 55% <sup>i</sup> (45-62%)	NA
	400 mg po q12h days 2-7	300 mg qd x 7 days	NA	↑ 23% <sup>i</sup> (↓ 1-↑ 53%)	↓ 7% <sup>i</sup> (↓ 23-↑ 13%)	NA
Atorvastatin	10 mg qd x 4 days	600 mg qd x 15 days	14	↓ 14% (1-26%)	↓ 43% (34-50%)	↓ 69% (49-81%)
Total active (including metabolites)				↓ 15% (2-26%)	↓ 32% (21-41%)	↓ 48% (23-64%)

Pravastatin	40 mg qd x 4 days	600 mg qd x 15 days	13	↓ 32% (↓ 59-↑ 12%)	↓ 44% (26-57%)	↓ 19% (0-35%)
Simvastatin	40 mg qd x 4 days	600 mg qd x 15 days	14	↓ 72% (63-79%)	↓ 68% (62-73%)	↓ 45% (20-62%)
Total active (including metabolites)				↓ 68% (55-78%)	↓ 60% (52-68%)	NA <sup>j</sup>
Carbamazepine	200 mg qd x 3 days, 200 mg bid x 3 days, then 400 mg qd x 29 days	600 mg qd 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 qd x 10 days	11	↓ 24% (18-30%)	↔	NA
Diltiazem	240 mg x 21 days	600 mg qd 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-monodes- methyl diltiazem				↓ 28% (7-44%)	↓ 37% (17-52%)	↓ 37% (17-52%)
Ethinyl estradiol/ Norgestimate	0.035 mg/0.25 mg x 14 days	600 mg qd x 14 days				
Ethinyl estradiol			21	↔	↔	↔
Norelgestromin			21	↓ 46% (39-52%)	↓ 64% (62-67%)	↓ 82% (79-85%)
Levonorgestrel			6	↓ 80% (77-83%)	↓ 83% (79-87%)	↓ 86% (80-90%)
Lorazepam	2 mg single dose	600 mg qd x 10 days	12	↑ 16% (2-32%)	↔	NA
Methadone	Stable maintenance 35-100 mg daily	600 mg qd x 14-21 days	11	↓ 45% (25-59%)	↓ 52% (33-66%)	NA
Paroxetine	20 mg qd x 14 days	600 mg qd x 14 days	16	↔	↔	↔
Sertraline	50 mg qd x 14 days	600 mg qd 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%

<sup>a</sup> Compared with atazanavir 400 mg q.d. alone.

<sup>b</sup> Comparator dose of indinavir was 800 mg q8h × 10 days.

<sup>c</sup> Parallel-group design; n for efavirenz + lopinavir/ritonavir, n for lopinavir/ritonavir alone.

<sup>d</sup> Values are for lopinavir; the pharmacokinetics of ritonavir 100 mg q12h is unaffected by concurrent efavirenz.

<sup>e</sup> 95% CI.

<sup>f</sup> Soft Gelatin Capsule.

<sup>g</sup> Tenofovir disoproxil fumarate.

<sup>h</sup> 95% CI not available

<sup>i</sup> Relative to steady-state administration of voriconazole (400 mg for 1 day, then 200 mg po q12h for 2 days).

<sup>j</sup> Not available because of insufficient data.

NA = not available.

**Table 8: Effect of Co-administered Drug on Efavirenz Plasma C<sub>max</sub>, AUC and C<sub>min</sub>**

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Efavirenz (mean % change)		
				C <sub>max</sub> (90% CI)	AUC (90% CI)	C <sub>min</sub> (90% CI)
Indinavir	800 mg q8h x 14 days	200 mg qd x 14 days	11	↔	↔	↔
Lopinavir/ ritonavir	400/100 mg q12h x 9 days	600 mg qd x 9 days	11,12 <sup>a</sup>	↔	↓ 16% (↓ 38-↑ 15%)	↓ 16% (↓ 42-↑ 20%)
Nelfinavir	750 mg q8h x 7 days	600 mg qd x 7 days	10	↓ 12% (↓ 32-↑ 13%) <sup>b</sup>	↓ 12% (↓ 35-↑ 18%) <sup>b</sup>	↓ 21% (↓ 53-↑ 33%)
Ritonavir	500 mg q12h x 8 days	600 mg qd x 10 days	9	↑ 14% (4-26%)	↑ 21% (10-34%)	↑ 25% (7-46%) <sup>b</sup>
Saquinavir <sup>c</sup> SGC <sup>e</sup>	1200 mg q8h x 10 days	600 mg qd x 10 days	13	↓ 13% (5-20%)	↓ 12% (4-19%)	↓ 14% (2-24%) <sup>b</sup>
Tenofovir <sup>d</sup>	300 mg qd	600 mg qd x 14 days	30	↔	↔	↔
Azithromycin	600 mg single dose	400 mg qd x 7 days	14	↔	↔	↔
Clarithromycin	500 mg q12h x 7 days	400 mg qd x 7 days	12	↑ 11% (3-19%)	↔	↔
Fluconazole	200 mg x 7 days	400 mg qd x 7 days	10	↔	↑ 16% (6-26%)	↑ 22% (5-41%)
Itraconazole	200 mg q12h x 14 days	600 mg qd x 28 days	16	↔	↔	↔
Rifabutin	300 mg qd x 14 days	600 mg qd x 14 days	11	↔	↔	↓ 12% (↓ 24-↑ 1%)
Rifampin	600 mg x 7 days	600 mg qd x 7 days	12	↓ 20% (11-28%)	↓ 26% (15-36%)	↓ 32% (15-46%)
Voriconazole	400 mg po q12h x 1 day, then 200 mg po q12h x 8 days	400 mg qd x 9 days	NA	↑ 38% <sup>e</sup>	↑ 44% <sup>e</sup>	NA
	300 mg po q12h days 2-7	300 mg qd x 7 days	NA	↓ 14% <sup>f</sup> (7-21%)	↔ <sup>f</sup>	NA
	400 mg po q12h days 2-7	300 mg qd x 7 days	NA	↔ <sup>f</sup>	↑ 17% <sup>f</sup> (6-29%)	NA
Atorvastatin	10 mg qd x 4 days	600 mg qd x 15 days	14	↔	↔	↔

Pravastatin	40 mg qd x 4 days	600 mg qd x 15 days	11	↔	↔	↔
Simvastatin	40 mg qd x 4 days	600 mg qd 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 qd x 35 days	14	↓ 21% (15-26%)	↓ 36% (32-40%)	↓ 47% (41-53%)
Cetirizine	10 mg single dose	600 mg qd x 10 days	11	↔	↔	↔
Diltiazem	240 mg x 14 days	600 mg qd x 28 days	12	↑ 16% (6-26%)	↑ 11% (5-18%)	↑ 13% (1-26%)
Famotidine	40 mg single dose	400 mg single dose	17	↔	↔	NA
Paroxetine	20 mg qd x 14 days	600 mg qd x 14 days	12	↔	↔	↔
Sertraline	50 mg qd x 14 days	600 mg qd x 14 days	13	↑ 11% (6-16%)	↔	↔

↑ Indicates increase; ↓ Indicates decrease; ↔ Indicates no change or a mean increase or decrease of <10%.

<sup>a</sup> Parallel-group design; n for efavirenz + lopinavir/ritonavir, n for efavirenz alone. <sup>b</sup> 95% CI.

<sup>c</sup> Soft Gelatin Capsule.

<sup>d</sup> Tenofovir disoproxil fumarate.

<sup>e</sup> 90% CI not available.

<sup>f</sup> Relative to steady-state administration of efavirenz (600 mg once daily for 9 days).

NA = not available.

### **Lactic Acidosis/Severe Hepatomegaly with Steatosis/ Hepatic Failure**

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination, including lamivudine 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 lamivudine 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 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).

### **Patients with HIV-1 and Hepatitis B Virus Co-infection**

#### ***Post-Treatment Exacerbations of Hepatitis***

In clinical trials in non-HIV-1-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 the re-emergence of HBV DNA. Although most events appear to have been self-limited, fatalities have been reported in some cases. Similar events have been reported from postmarketing experience after changes from lamivudine-containing HIV-1 treatment regimens to non-lamivudine-containing regimens in patients infected with both HIV-1 and HBV. The causal relationship to discontinuation of lamivudine treatment is unknown. Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. There is insufficient evidence to determine whether re-initiation of lamivudine alters the course of post-treatment exacerbations of hepatitis.

### ***Important Differences Among Lamivudine-Containing Products***

**LAMIVIR** Tablets and Oral Solution contain a higher dose of the same active ingredient (lamivudine) than **LAMIVIR-HBV Tablets**. **LAMIVIR-HBV** was developed for patients with chronic hepatitis B. The formulation and dosage of lamivudine in **LAMIVIR-HBV** are not appropriate for patients co-infected with HIV-1 and HBV. Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients co-infected with HIV-1 and HBV. If treatment with **LAMIVIR-HBV** is prescribed for chronic hepatitis B for a patient with unrecognized or untreated HIV-1 infection, rapid emergence of HIV-1 resistance is likely to result because of the subtherapeutic dose and the inappropriateness of monotherapy HIV-1 treatment. If a decision is made to administer lamivudine to patients co-infected with HIV-1 and HBV, lamivudine should be used as part of an appropriate combination regimen.

### ***Emergence of Lamivudine-Resistant HBV:***

In non-HIV-1-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 -1 -infected patients who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus.

### ***Use with Other Lamivudine- and Emtricitabine-Containing Products***

Lamivudine should not be administered concomitantly with other lamivudine- or emtricitabine containing products.

### ***Use with Interferon- and Ribavirin-Based Regimens***

*In vitro* studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (eg, loss of HIV-1/HCV virologic suppression) was seen when ribavirin was co-administered with lamivudine in HIV-1/HCV co-infected patients (see **PHARMACOLOGY**), hepatic decompensation (some fatal) has occurred

in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin. Patients receiving interferon alfa with or without ribavirin and lamivudine should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of lamivudine 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 (eg, Childs Pugh >6).

### **Pancreatitis**

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

### **Stavudine**

#### **Hepatic Impairment and Toxicity**

The safety and efficacy of stavudine have not been established in HIV-infected patients with significant underlying liver disease. During combination antiretroviral therapy, patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities, including severe and potentially fatal hepatic adverse events, and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

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

#### **Use with Interferon- and Ribavirin-Based Regimens**

*In vitro* studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as stavudine. Although no evidence of a pharmacokinetic or pharmacodynamic (eg, loss of HIV/HCV virologic suppression) interaction was seen when ribavirin was co-administered with stavudine in HIV/HCV co-infected patients, **hepatic decompensation (some fatal) has occurred in HIV/HCV co-infected patients receiving combination antiretroviral therapy for HIV and interferon and ribavirin.** Patients receiving interferon with or without ribavirin and stavudine should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of stavudine should be considered as medically appropriate. Dose reduction or discontinuation of interferon, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (eg, Child-Pugh >6) (see the complete prescribing information for interferon and ribavirin).

## **Neurologic Symptoms**

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

Peripheral neuropathy, manifested by numbness, tingling, or pain in the hands or feet, has been reported in patients receiving stavudine therapy. Peripheral neuropathy has occurred more frequently in patients with advanced HIV disease, a history of neuropathy, or concurrent neurotoxic drug therapy, including didanosine (see **UNDESIRABLE EFFECTS**).

## **Pancreatitis**

Fatal and non-fatal pancreatitis have occurred during therapy when stavudine was part of a combination regimen that included didanosine in both treatment-naïve and treatment-experienced patients, regardless of the degree of immunosuppression. The combination of stavudine and didanosine and any other agents that are toxic to the pancreas should be suspended in patients with suspected pancreatitis. Reinstitution of stavudine after a confirmed diagnosis of pancreatitis should be undertaken with particular caution and close patient monitoring. The new regimen should contain neither didanosine.

## **Resistance**

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. 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.

## **Co-administration with Related Products**

Coadministration of efavirenz with combination of efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg is not recommended, since efavirenz is one of its active ingredients.

## **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 (regardless of causality) 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%), non-fatal 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 a 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 **UNDESIRABLE EFFECTS**).

### **Nervous System Symptoms**

53%(531/1008) of patients receiving efavirenz reported central nervous system symptoms (any grade, regardless of causality) compared to 25% (156/635) of patients receiving control regimens. These symptoms included, but were not limited to, dizziness (28.1% of the 1008 patients), 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 AND PRECAUTIONS**). Dosing at bedtime may improve the tolerability of these nervous system symptoms (see **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.

### **Rash**

In controlled clinical trials, 26% (266/1008) of patients treated with 600 mg efavirenz experienced new-onset rash compared with 17% (111/635) of patients treated in control groups. Rash associated with blistering, moist desquamation or ulceration occurred in 0.9% of patients treated with efavirenz. The incidence of Grade 4 rash (eg, erythema multiforme or Stevens-Johnson syndrome) in patients treated with efavirenz in all studies and expanded access was 0.1%. Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first 2 weeks of initiating therapy with efavirenz (median time to onset of rash in adults was 11 days) and, in most patients continuing therapy with efavirenz, rash resolves within 1 month (median duration, 16 days). The discontinuation rate for rash in clinical trials was 1.7% (17/1008). Efavirenz can be reinitiated in patients interrupting therapy because of rash. 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. (see **UNDESIRABLE EFFECTS**). One pediatric patient experienced Grade 3 rash (confluent rash with fever), and 2 patients had Grade 4 rash (erythema multiforme). The median time to onset of rash in pediatric patients was 8 days. Prophylaxis with appropriate antihistamines before initiating therapy with efavirenz in pediatric patients should be considered.

### **Hepatotoxicity**

Monitoring of liver enzymes before and during treatment is recommended for patients with underlying hepatic disease, including hepatitis B or C infection; patients with marked transaminase elevations; and patients treated with other medications associated with liver toxicity (see **UNDESIRABLE EFFECTS**). A few of the postmarketing reports of hepatic failure occurred in patients with no pre-existing hepatic disease or other identifiable risk factors (see **UNDESIRABLE EFFECTS**). Liver enzyme monitoring should also be considered for patients without pre-existing hepatic dysfunction or other risk factors. 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.

## Convulsions

Convulsions have been observed in patients receiving efavirenz, generally in the presence of known medical history of seizures. Caution must be taken in any patient with a 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 **DRUG INTERACTIONS**).

## Lipid Elevations

Treatment with efavirenz has resulted in increases in the concentration of total cholesterol and triglycerides. (see **UNDESIRABLE EFFECTS**). Cholesterol and triglyceride testing should be performed before initiating efavirenz therapy and at periodic intervals during therapy.

## Immune Reconstitution Syndrome

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

## 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.

## Renal Impairment

**Lamivudine and stavudine:** Reduction of the dosage of both stavudine and lamivudine is required in patients with a creatinine clearance of 50 ml/min or less. Hence, **LAMIVIR-SE 30/ KIT** cannot be used in this patient population.

**Efavirenz:** The pharmacokinetics of efavirenz has not been studied in patients with renal insufficiency. However, less than 1% of efavirenz is excreted unchanged in the urine, so the impact of renal impairment on efavirenz elimination should be minimal.

## Hepatic Impairment

The pharmacokinetics of efavirenz has not been adequately studied in patients with hepatic impairment. 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 (see **WARNINGS AND PRECAUTIONS**).

### **Pregnancy**

**Lamivudine and stavudine:** Pregnancy category C. Both lamivudine and stavudine are classified under category C. There are no adequate and well-controlled studies in pregnant women. Animal reproduction studies in rats and rabbits revealed no evidence of teratogenicity. Increased early embryoletality occurred in rabbits at exposure levels similar to those in humans. Lamivudine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lamivudine pharmacokinetics was studied in pregnant women during 2 clinical studies conducted in South Africa. The study assessed pharmacokinetics in 16 women at 36 weeks gestation using 150 mg lamivudine twice daily with zidovudine; 10 women at 38 weeks gestation using 150 mg lamivudine twice daily with zidovudine; and 10 women at 38 weeks gestation using lamivudine 300 mg twice daily without other antiretrovirals. These studies were not designed or powered to provide efficacy information. Lamivudine pharmacokinetics in the pregnant women was similar to those seen in non-pregnant adults and in postpartum women. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples. In a subset of subjects, lamivudine amniotic fluid specimens were collected following the natural rupture of the membranes. Amniotic fluid concentrations of lamivudine were typically 2 times greater than maternal serum levels and ranged from 1.2 to 2.5 mcg/mL (150 mg twice daily) and 2.1 to 5.2 mcg/mL (300 mg twice daily).

It is not known whether the risk of adverse events associated with lamivudine are altered in pregnant women compared with other HIV-1-infected patients. Animal reproduction studies performed at oral doses up to 130 and 60 times the adult dose in rats and rabbits, respectively, revealed no evidence of teratogenicity due to lamivudine. Increased early embryoletality occurred in rabbits at exposure levels similar to those in humans. However, there was no indication of this effect in rats at exposure levels up to 35 times those in humans. Based on animal studies, lamivudine crosses the placenta and is transferred to the fetus.

Reproduction studies have been performed in rats and rabbits with exposures (based on C<sub>max</sub>) up to 399 and 183 times, respectively, of that seen at a clinical dosage of 1 mg/kg/day and have revealed no evidence of teratogenicity. The incidence in fetuses of a common skeletal variation, unossified or incomplete ossification of sternebra, was increased in rats at 399 times human exposure, while no effect was observed at 216 times human exposure. A slight post-implantation loss was noted at 216 times the human exposure with no effect noted at approximately 135 times the human exposure. An increase in early rat neonatal mortality (birth to 4 days of age) occurred at 399 times the human exposure, while survival of neonates was unaffected at approximately 135 times the human exposure. A study in rats showed that stavudine is transferred to the fetus through the placenta. The concentration in fetal tissue was approximately one-half the concentration in maternal plasma. Animal reproduction studies are not always predictive of human response.

There are no adequate and well-controlled studies of stavudine in pregnant women. Stavudine should be used during pregnancy only if the potential benefit justifies the risk.

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

## **Efavirenz:**

### ***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 (eg, oral or other hormonal contraceptives). Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of efavirenz is recommended. 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.

### **Lactation**

The Centers for Disease Control and Prevention recommend that HIV-1 infected mothers do not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. Studies in lactating rats demonstrated that stavudine is excreted in breast milk. Although it is not known whether stavudine is excreted in human milk, there exists the potential for adverse effects from stavudine in nursing infants. Although it is not known if efavirenz is secreted in human milk, efavirenz is secreted into the milk of lactating rats.

Because of the potential for serious adverse reactions in nursing infants and HIV-1 transmission, mothers should be instructed not to breastfeed if they are receiving lamivudine. Lamivudine is excreted in human milk. Samples of breast milk obtained from 20 mothers receiving lamivudine monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice daily and 300 mg zidovudine twice daily) had measurable concentrations of lamivudine.

### **Geriatric Use**

Clinical studies of lamivudine, stavudine and efavirenz did not include a 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. Greater sensitivity of some elderly individuals to the effects of stavudine cannot be ruled out. In particular, because lamivudine is substantially excreted by the kidneys and elderly patients are more likely to have decreased renal function, renal function should be monitored and dosage adjustments should be made accordingly (see **DOSAGE AND ADMINISTRATION AND PHARMACOLOGY**).

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

Stavudine is known to be substantially excreted by the kidneys, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function. Dose adjustment is recommended for patients with renal impairment (see **DOSAGE AND ADMINISTRATION, Dosage Adjustment**).

**Pediatrics**

**LAMIVIR-SE 30/ KIT** is not intended for use in pediatric patients.

**UNDESIRABLE EFFECTS**

***Lamivudine***

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

**Adults**

The safety profile of lamivudine in adults is primarily based on 3,568 HIV-1 infected patients in 7 clinical trials. The most common adverse reactions are headache, nausea, malaise, fatigue, nasal signs and symptoms, diarrhea and cough.

Selected clinical adverse reactions of in  $\geq 5\%$  of patients during therapy with lamivudine 150 mg twice daily plus zidovudine 200 mg 3 times daily for up to 24 weeks are listed in Table 9.

**Table 9: Selected Clinical Adverse Events ( $\geq 5\%$  Frequency) in Four Controlled Clinical Trials (NUCA3001, NUCA3002, NUCB3001, NUCB3002)**

<b>Adverse Reaction</b>	<b>Lamivudine 150 mg twice daily plus Zidovudine (n = 251)</b>	<b>Zidovudine* (n = 230)</b>
<b>Body as a Whole</b>		
Headache	35%	27%
Malaise and fatigue	27%	23%
Fever or chills	10%	12%
<b>Digestive</b>		

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

\*Either zidovudine monotherapy or zidovudine in combination with zalcitabine.

Pancreatitis was observed in 9 of the 2613 adult patients (0.3%) who received lamivudine in the controlled clinical trials EPV20001, NUCA3001, NUCB3001, NUCA3002, NUCB3002, and NUCB3007.(see **WARNINGS AND PRECAUTIONS**).

The types and frequencies of clinical adverse reactions reported in patients receiving lamivudine 300 mg once daily or lamivudine 150 mg twice daily (in 3-drug combination regimens in EPV20001 AND EPV40001) for 48 weeks were similar.

Selected laboratory abnormalities observed during therapy are summarized in Table 10.

**Table 10: Frequencies of Selected Grade 3–4 Laboratory Abnormalities in Adults in Four 24-Week Surrogate Endpoint Studies (NUCA3001, NUCA3002, NUCB3001, NUCB3002) and a Clinical Endpoint Study (NUCB3007)**

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

\* The median duration on study was 12 months.

† Either zidovudine monotherapy or zidovudine in combination with zalcitabine.

‡ Current therapy was zidovudine, or zidovudine plus didanosine, or zidovudine plus zalcitabine.

ULN = Upper limit of normal.

ND = Not done.

The frequencies of selected laboratory abnormalities reported in patients receiving lamivudine 300 mg once daily or lamivudine 150 mg twice daily (in 3-drug combination regimens in EPV20001 and EPV40001) were similar.

### **Pancreatitis**

Pancreatitis, which has been fatal in some cases, has been observed in antiretroviral nucleoside-experienced pediatric patients receiving lamivudine alone or in combination

with other antiretroviral agents. In an open-label, dose-escalation study (NUCA2002), 14 patients (14%) developed pancreatitis while receiving monotherapy with lamivudine. Three of these, 3 patients died of complications of pancreatitis. In a second open-label study (NUCA2005), 12 patients (18%) developed pancreatitis. In Study ACTG300, pancreatitis was not observed in 236 patients randomized to lamivudine plus zidovudine. Pancreatitis was observed in 1 patient in this study who received open-label lamivudine in combination with zidovudine and ritonavir following discontinuation of didanosine monotherapy (see **WARNINGS AND PRECAUTIONS**).

#### **Observed During Clinical Practice**

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been reported during post-marketing use of lamivudine. Because these reactions are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These reactions have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to lamivudine.

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

**Endocrine and Metabolic:** Hyperglycemia.

**General:** Weakness.

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

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

**Hypersensitivity:** Anaphylaxis, urticaria.

**Musculoskeletal:** Muscle weakness, CPK elevation, rhabdomyolysis.

**Skin:** Alopecia, pruritus.

#### **Stavudine**

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

Stavudine therapy has rarely been associated with motor weakness, occurring predominantly in the setting of lactic acidosis. If motor weakness develops, stavudine should be discontinued.

Stavudine therapy has also been associated with peripheral sensory neuropathy, which can be severe, is dose-related, and occurs more frequently in patients being treated with other drugs that have been associated with neuropathy (including didanosine), in patients with advanced HIV infection, or in patients who have previously experienced peripheral neuropathy.

Patients should be monitored for the development of neuropathy, which is usually manifested by numbness, tingling, or pain in the feet or hands. Stavudine-related peripheral neuropathy may resolve if therapy is withdrawn promptly. In some cases, symptoms may worsen temporarily following discontinuation of therapy. If symptoms resolve completely, patients may tolerate resumption of treatment at one-half of the dose (see **DOSAGE AND ADMINISTRATION**). If neuropathy recurs after resumption, permanent discontinuation of stavudine should be considered.

Selected clinical adverse events that occurred in adult patients receiving stavudine in a controlled monotherapy study (Study AI455-019) are provided in Table 11.

**Table 11: Selected Clinical Adverse Events in Study AI455-019<sup>a</sup> (Monotherapy)**

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

<sup>a</sup> Any severity, regardless of relationship to study drug

<sup>b</sup> Median duration of stavudine therapy = 79 weeks, median duration of zidovudine therapy = 53 weeks

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

Selected clinical adverse events that occurred in antiretroviral-naïve adult patients receiving stavudine in two controlled combination studies are provided in Table 12.

**Table 12: Selected Clinical Adverse Events in START 1 and START 2 Studies (Combination Therapy)**

Adverse events	Percent (%)			
	START 1		START 2 <sup>b</sup>	
	Stavudine + lamivudine + indinavir (n = 100) <sup>c</sup>	Zidovudine + lamivudine + indinavir (n = 102)	Didanosine + indinavir (n=102) <sup>c</sup>	Zidovudine + lamivudine + indinavir (n = 103)
Nausea	43	63	53	67
Diarrhea	34	16	45	39
Headache	25	26	46	37
Rash	18	13	30	18
Vomiting	18	33	30	35
Peripheral Neurologic Symptoms/Neuropathy	8	7	21	10

<sup>a</sup> Any severity, regardless of relationship to study regimen

<sup>b</sup> START 2 compared two triple-combination regimens in 205 treatment-naïve patients. Patients receive either Stavudine (40 mg twice daily) plus didanosine plus indinavir or zidovudine plus lamivudine plus indinavir

<sup>c</sup>Duration of stavudine therapy=48 weeks

Pancreatitis resulting in death was observed in patients treated with stavudine plus didanosine in controlled clinical studies and in postmarketing reports.

Selected laboratory abnormalities reported in a controlled monotherapy study (Study AI455-019) are provided in Table 13.

**Table 13 : Selected Adult Laboratory Abnormalities in Study AI455-019<sup>a, b</sup>**

Parameter	Percent (%)	
	stavudine (40 mg twice daily) (n=412)	zidovudine (200 mg 3 times daily) (n=402)
AST (SGOT) (>5.0 x ULN)	11	10
ALT (SGPT) (>5.0 x ULN)	13	11
Amylase (≥1.4 x ULN)	14	13

<sup>a</sup> Data presented for patients for whom laboratory evaluations were performed.

<sup>b</sup> Median duration of stavudine therapy = 79 weeks; median duration of zidovudine therapy = 53 weeks.

ULN = upper limit of normal.

Selected laboratory abnormalities reported in two controlled combination studies are provided in Tables 14 and 15.

**Table 14: Selected Laboratory Abnormalities in START 1 and START 2 Studies (Grades 3-4)**

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

ULN = upper limit of normal.

**Table 15: Selected Laboratory Abnormalities in START 1 and START 2 Studies (All Grades)**

Parameter	Percent (%)			
	START 1		START 2	
	Stavudine +	Zidovudine +	Stavudine +	Zidovudine +

	<b>lamivudine + indinavir (n=100)</b>	<b>lamivudine + indinavir (n=102)</b>	<b>didanosine + indinavir (n=102)</b>	<b>lamivudine + indinavir (n=103)</b>
Total Bilirubin	65	60	68	55
AST (SGOT)	42	20	53	20
ALT (SGPT)	40	20	50	18
GGT	15	8	28	12
Lipase	27	12	26	19
Amylase	21	19	31	17

**Observed During Clinical Practice:**

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

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

**Digestive Disorders:** Anorexia

**Exocrine Gland Disorders:** Pancreatitis (including fatal cases) (see **WARNINGS AND PRECAUTIONS**)

**Hematologic Disorders:** Anemia, leukopenia, and thrombocytopenia and macrocytosis

**Liver:** Symptomatic hyperlactatemia/lactic acidosis and hepatic steatosis (see **WARNINGS AND PRECAUTIONS**), hepatitis and liver failure

**Metabolic Disorders**—diabetes mellitus and hyperglycemia.

**Musculoskeletal:** Myalgia

**Nervous System:** Insomnia, severe motor weakness (most often reported in the setting of lactic acidosis) (see **WARNINGS AND PRECAUTIONS**)

**Use with Didanosine- and Hydroxyurea-Based Regimens**

When stavudine is used in combination with other agents with similar toxicities, the incidence of these toxicities may be higher than when stavudine is used alone. Thus, patients treated with stavudine in combination with didanosine, with or without hydroxyurea, may be at increased risk for pancreatitis and hepatotoxicity, which may be fatal, and severe peripheral neuropathy. The combination of stavudine and

hydroxyurea, with or without didanosine, should be avoided (see **WARNINGS** and **PRECAUTIONS**).

**Efavirenz:**

The most common (>5% in either efavirenz treatment group) adverse reactions of at least moderate severity among patients in Study 006 treated with efavirenz in combination with zidovudine / lamivudine or indinavir were rash, dizziness, nausea, headache, fatigue, insomnia, and vomiting.

**Clinical Trials Experience in Adults**

Because clinical studies are conducted under widely varying conditions, the adverse reaction rates reported cannot be directly compared to rates in other clinical studies and may not reflect the rates observed in clinical practice.

Selected clinical adverse reactions of moderate or severe intensity observed in ≥2% of efavirenz-treated patients in two controlled clinical trials are presented in Table 16.

**Table 16: Selected Treatment-Emergent <sup>a</sup> Adverse Reactions of Moderate or Severe Intensity Reported in ≥2% of Efavirenz-Treated Patients in Studies 006 and ACTG 364**

Adverse Reactions	Study 006			Study ACTG 364		
	LAM-, NNRTI-, and Protease Inhibitor-Naïve Patients			NRTI-Experienced, NNRTI-and Protease Inhibitor-Naïve Patients		
	Efavirenz <sup>b</sup> + ZDV/LAM  (n=412) 180 weeks <sup>c</sup>	Efavirenz <sup>b</sup> + Indinavir  (n=415) 102 weeks <sup>c</sup>	Indinavir + ZDV/LAM  (n=401) 76 weeks <sup>c</sup>	Efavirenz <sup>b</sup> + Nelfinavir + NRTIs  (n=64) 71.1 weeks <sup>c</sup>	Efavirenz + NRTIs  (n=65) 70.9 weeks <sup>c</sup>	Nelfinavir + NRTIs  (n=66) 62.7 weeks <sup>c</sup>
<b>Body as a Whole</b>						
Fatigue	8%	5%	9%	0	2%	3%
Pain	1%	2%	8%	13%	6%	17%
<b>Central and Peripheral Nervous System</b>						
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%
<b>Gastrointestinal</b>						
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%
<b>Psychiatric</b>						
Anxiety	2%	4%	<1%	–	–	–
Depression	5%	4%	<1%	3%	0	5%
Nervousness	2%	2%	0	2%	0	2%
<b>Skin and Appendages</b>						
Rash <sup>d</sup>	11%	16%	5%	9%	5%	9%
Pruritus	<1%	1%	1%	9%	5%	9%

<sup>a</sup> Includes adverse events at least possibly related to the study drug or of unknown relationship for Study 006. Includes all adverse events regardless of relationship to study drug for Study ACTG 364.

<sup>b</sup> Efavirenz provided as 600 mg once daily.

<sup>c</sup> Median duration of treatment.

<sup>d</sup> Includes erythema multiforme, rash, rash erythematous, rash follicular, rash maculopapular, rash petechial, rash pustular, and urticaria for Study 006 and macules, papules, rash, erythema, redness, inflammation, allergic rash, urticaria, welts, hives, itchy, and pruritus for ACTG 364.

– = Not Specified.

ZDV = Zidovudine; LAM = Lamivudine

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 **UNDESIRABLE EFFECTS, Laboratory Abnormalities**).

## Nervous System Symptoms

For 1008 patients treated with regimens containing efavirenz and 635 patients treated with a control regimen in controlled trials, Table 7 lists the frequency of 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. (see **WARNINGS AND PRECAUTIONS**). The frequencies of specific central and peripheral nervous system symptoms are provided in Table 17.

**Table 17: Percent of Patients with One or More Selected Nervous System Symptoms**<sup>a, b</sup>

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 <sup>c</sup>	33.3	15.6
Moderate symptoms <sup>d</sup>	17.4	7.7
Severe symptoms <sup>e</sup>	2.0	1.3
Treatment discontinuation as a result of symptoms	2.1	1.1

<sup>a</sup> Includes events reported regardless of causality.

<sup>b</sup> Data from Study 006 and three Phase 2/3 studies.

<sup>c</sup> "Mild" = Symptoms which do not interfere with a patient's daily activities.

<sup>d</sup> "Moderate" = Symptoms which may interfere with daily activities

<sup>e</sup> "Severe" = Events which interrupt a patient's usual daily activities.

## Psychiatric Symptoms

Serious psychiatric adverse experiences have been reported in patients treated with efavirenz. In controlled trials, psychiatric symptoms observed at a frequency of >2% among patients treated with efavirenz or control regimens, respectively, were depression (19%, 16%), anxiety (13%, 9%) and nervousness (7%, 2%).

## Rash

For 1008 adults and 57 pediatric patients treated with regimens containing efavirenz and 635 patients treated with a control regimen in controlled trials, the frequency of rash by NCI grade and the discontinuation rates as a result of rash in clinical studies are provided in Table 18 (see **WARNINGS AND PRECAUTIONS**).

**Table 18: Percent of Patients with Treatment-Emergent Rash**<sup>a, b</sup>

Percent of Patients with:	Description of Rash Grade <sup>c</sup>	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

<sup>a</sup> Includes events reported regardless of causality.

<sup>b</sup> Data from Study 006 and three Phase 2/3 studies.

<sup>c</sup> NCI Grading System.

As seen in Table 8, rash is more common in pediatric patients and more often of higher grade (ie, more severe).(see **WARNINGS AND 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. 9 of these patients developed mild – to - moderate rash while receiving therapy with efavirenz, and 2 of these patients discontinued because of rash.

### Laboratory Abnormalities

Selected Grade 3–4 laboratory abnormalities reported in  $\geq 2\%$  of efavirenz-treated patients in two clinical trials are presented in Table 19.

**Table 19: Selected Grade 3-4 Laboratory Abnormalities Reported in  $\geq 2\%$  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		
		Efavirenz <sup>a</sup> +ZDV/LAM (n=412)	Efavirenz <sup>a</sup> + Indinavir (n=415)	Indinavir + ZDV/ LAM (n=401)	Efavirenz <sup>a</sup> + Nelfinavir + NRTIs (n=64)	Efavirenz <sup>a</sup> + NRTIs (n=65)	Nelfinavir + NRTIs (n=66)
Variable	Limit	180 weeks <sup>b</sup>	102 weeks <sup>b</sup>	76 weeks <sup>b</sup>	71.1 weeks <sup>b</sup>	70.9 weeks <sup>b</sup>	62.7 weeks
<b>Chemistry</b>							
ALT	>5 × ULN	5%	8%	5%	2%	6%	3%
AST	>5 × ULN	5%	6%	5%	6%	8%	8%
GGT <sup>c</sup>	>5 × ULN	8%	7%	3%	5%	0	5%
Amylase	>2 × ULN	4%	4%	1%	0	6%	2%
Glucose	>250 mg/dL	3%	3%	3%	5%	2%	3%
Triglycerides <sup>d</sup>	$\geq 751$ mg/dL	9%	6%	6%	11%	8%	17%
<b>Hematology</b>							
Neutrophils	<750/mm <sup>3</sup>	10%	3%	5%	2%	3%	2%

<sup>a</sup> Efavirenz provided as 600 mg once daily.

<sup>b</sup> Median duration of treatment.

<sup>c</sup> Isolated elevations of GGT in patients receiving efavirenz may reflect enzyme induction not associated with liver toxicity.

<sup>d</sup> Nonfasting.

ZDV = Zidovudine, LAM = Lamivudine, ULN = Upper limit of normal, ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, GGT = Gamma-glutamyltransferase

### **Patients Coinfected with Hepatitis B or C**

Liver function tests should be monitored in patients with a history of hepatitis B and/or C. In the long-term data set from Study 006, 137 patients treated with efavirenz-containing regimens (median duration of therapy, 68 weeks) and 84 treated with a control regimen (median duration, 56 weeks) were seropositive at screening for hepatitis B (surface antigen positive) and/or C (hepatitis C antibody positive). Among these co-infected patients, elevations in AST to greater than five times the 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 the 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 **WARNINGS AND 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 non-fasting total cholesterol and high-density lipids (HDL) of approximately 20% and 25%, respectively, were observed. In patients treated with efavirenz + indinavir, increases from baseline in non-fasting cholesterol and HDL of approximately 40% and 35%, respectively, were observed. Non-fasting total cholesterol levels  $\geq 240$  mg/dL and  $\geq 300$  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 in this study were not well characterized since samples were taken from nonfasting patients. The clinical significance of these findings is unknown. (see **WARNINGS AND PRECAUTIONS**).

### **Clinical Trial Experience in Pediatric Patients**

Clinical adverse experiences observed in  $\geq 10\%$  of 57 pediatric patients aged 3 to 16 years who received efavirenz capsules, nelfinavir, and one or more NRTIs in Study ACTG 382 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 **WARNINGS AND PRECAUTIONS AND UNDESIRABLE EFFECTS**).

### **Observed During Clinical Practice**

The following adverse reactions have been identified during postapproval use of efavirenz. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**Body as a Whole:** Allergic reactions, asthenia, redistribution/accumulation of body fat. (see **WARNINGS AND PRECAUTIONS**).

**Central and Peripheral Nervous System:** Abnormal coordination, ataxia, cerebellar coordination and balance disturbances, convulsions, hypoesthesia, paresthesia, neuropathy, tremor.

**Endocrine:** Gynecomastia.

**Gastrointestinal:** Constipation, malabsorption.

**Cardiovascular:** Flushing, palpitations.

**Liver and Biliary System:** Hepatic enzyme increase, hepatic failure, hepatitis. A few of the postmarketing reports of hepatic failure, including cases in patients with no pre-existing hepatic disease or other identifiable risk factors, were characterized by a fulminant course, progressing in some cases to transplantation or death.

**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, photoallergic dermatitis, skin discoloration, Stevens-Johnson syndrome.

**Special Senses:** Abnormal vision, tinnitus.

## **OVERDOSAGE**

### **Lamivudine**

There is no known antidote for lamivudine. One case of an adult ingesting 6 g of lamivudine was reported; there were no clinical signs or symptoms noted and hematologic tests remained normal. Two cases of pediatric overdose have been reported. One case involved was of a single dose of 7 mg/kg of lamivudine; the second case involved the use of 5 mg/kg of lamivudine twice daily for 30 days. There were no clinical signs or symptoms noted in either case. Because a negligible amount of lamivudine was removed via 4-hour hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event. If overdose occurs, the patient should be monitored, and standard supportive treatment applied as required.

### **Stavudine**

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

### **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 efavirenz. 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.

### **PACKAGING INFORMATION**

**LAMIVIR-SE KIT.....** Carton of 10 kits

*Last updated: October 2010*