

Efavirenz 600mg and Didanosine 250/400mg and Lamivudine 300mg Kit

#### **ODIVIR 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, DIDANOSINE AND OTHER ANTIRETROVIRALS (SEE WARNINGS AND PRECAUTIONS). SUSPEND TREATMENT IF CLINICAL OR LABORATORY FINDINGS SUGGESTIVE OF LACTIC ACIDOSIS OR PRONOUNCED HEPATOTOXICITY OCCUR (SEE WARNINGS AND PRECAUTIONS).**

**FATAL AND NON-FATAL PANCREATITIS HAS OCCURRED DURING THERAPY WITH DIDANOSINE USED ALONE OR IN COMBINATION REGIMENS IN BOTH TREATMENT-NAÏVE AND TREATMENT-EXPERIENCED PATIENTS, REGARDLESS OF THE DEGREE OF IMMUNOSUPPRESSION. DIDANOSINE CAPSULES SHOULD BE SUSPENDED IN PATIENTS WITH SUSPECTED PANCREATITIS AND DISCONTINUED IN PATIENTS WITH CONFIRMED PANCREATITIS (SEE WARNINGS AND PRECAUTIONS).**

**FATAL LACTIC ACIDOSIS HAS BEEN REPORTED IN PREGNANT WOMEN WHO RECEIVED THE COMBINATION OF DIDANOSINE AND STAVUDINE WITH OTHER ANTIRETROVIRAL AGENTS. THE COMBINATION OF DIDANOSINE AND STAVUDINE SHOULD BE USED WITH CAUTION DURING PREGNANCY AND IS RECOMMENDED ONLY IF THE POTENTIAL BENEFIT CLEARLY OUTWEIGHS THE POTENTIAL RISK (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. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE LAMIVUDINE AND ARE CO-INFECTED WITH HIV-1 AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS AND PRECAUTIONS).**

**ODIVIR-250 Kit**

Each kit contains:

(A) One Efavirenz tablet

Each film-coated tablet contains:

Efavirenz ..... 600 mg

(B) One Lamivudine tablet

Each film-coated tablet contains:

Lamivudine ..... 300 mg

(C) One Didanosine delayed-release capsule

Each capsule contains:

Didanosine ..... 250 mg (as enteric-coated beadlets)

**ODIVIR-400 Kit**

Each kit contains:

(A) One Efavirenz tablet

Each film-coated tablet contains

Efavirenz ..... 600 mg

(B) One Lamivudine tablet

Each film-coated tablet contains

Lamivudine ..... 300 mg

(C) One Didanosine delayed-release capsule

Each capsule contains:

Didanosine ..... 400 mg (as enteric-coated beadlets)

**DOSAGE FORMS**

Tablet and capsule

**DESCRIPTION**

Each **ODIVIR Kit** contains three pills and is designed to provide once-daily adult doses of three antiretroviral drugs. These drugs are efavirenz, lamivudine and didanosine. As per the current guidelines, this combination can be used as a once-daily triple drug regimen for the treatment of HIV-1 infection.

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.

Lamivudine is a synthetic nucleoside analog with activity against HIV-1. Lamivudine is the (–) enantiomer of a dideoxy analog of cytidine.

Didanosine is a synthetic purine nucleoside analog active against HIV-1. It is formulated as enteric-coated beadlets contained in a capsule. The enteric coating prevents degradation of didanosine by gastric acid. The enteric coating dissolves when the beadlets empty into the small intestine, the site of drug absorption.

## 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  $\gamma$ .

**Didanosine:** *Didanosine* is a synthetic nucleoside analog of the naturally occurring nucleoside, deoxyadenosine, in which the 3'-hydroxyl group is replaced by hydrogen. Intracellularly, didanosine is converted by cellular enzymes to the active metabolite, dideoxyadenosine 5'-triphosphate. Dideoxyadenosine 5'-triphosphate inhibits the activity of HIV-1 reverse transcriptase, both by competing with the natural substrate, deoxyadenosine 5'-triphosphate, and by its incorporation into viral DNA causing termination of viral DNA chain elongation.

**Efavirenz:** *Efavirenz* is a NNRTI of HIV-1. Efavirenz activity is mediated predominantly by the non-competitive inhibition of HIV-1 reverse transcriptase. HIV-2 reverse transcriptase and human cellular DNA polymerases,  $\alpha$ ,  $\beta$ ,  $\gamma$  or  $\delta$  are not inhibited by efavirenz.

### 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  $C_{max24,ss}$ ; 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  $\pm$  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% ± 1.4% (mean ± SD) of the dose was excreted as the trans-sulfoxide metabolite in the urine. Serum concentrations of this metabolite have not been determined.

**Elimination:** The majority of lamivudine is eliminated unchanged in urine by active organic cationic secretion. In 9 healthy subjects given a single 300 mg oral dose of lamivudine, renal clearance was 199.7 ± 56.9 mL/min (mean ± SD). In 20 HIV-1-infected patients given a single IV dose, renal clearance was 280.4 ± 75.2 ml/min (mean ± SD), representing 71% ± 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 ± 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.

### **Didanosine**

The pharmacokinetic parameters of didanosine in HIV-infected adult patients are summarized in Table 2, by weight ranges that correspond to recommended doses (Table 1). Didanosine is rapidly absorbed, with peak plasma concentrations generally observed from 0.25 to 1.50 hours following oral dosing with a buffered formulation. Increases in plasma didanosine concentrations were dose proportional over the range of 50 to 400 mg. In adults, the 319 mean (± standard deviation) oral bioavailability following single oral dosing with a buffered formulation is 42 (±12)%. After oral administration, the urinary recovery of didanosine is approximately 18 (±8)% of the dose. The CSF-plasma ratio following IV administration is 21 (±0.03)%. Steady-state pharmacokinetic parameters did not differ significantly from values 323 obtained after a single dose. Binding of didanosine to plasma proteins *in vitro* was low (less than 5%). Based on data from *in vitro* and animal studies, it is presumed that the metabolism of didanosine in man occurs by the same pathways responsible for the elimination of endogenous purines.

**Table 1: Pharmacokinetic Parameters for Didanosine in HIV-infected Patients**

Parameter <sup>a</sup>	Adults	
	At least 60 kg N = 7	At least 60 kg N = 44
Apparent clearance (L/h)	196.0 ± 55.8	174.5 ± 69.7
Apparent volume of	363 ± 137.7	308.3 ± 164.3

distribution (L)		
Elimination half-life (h)	1.26 ± 0.19	1.19 ± 0.21
Steady-state AUC (mg.h/L)	2.25 ± 0.89	2.65 ± 1.07

<sup>a</sup> The pharmacokinetic parameters (mean ± standard deviation) of didanosine were determined by a population pharmacokinetic model based on combined clinical studies.

### **Comparison of Didanosine Formulations**

The active ingredient, didanosine, is protected against degradation by stomach acid by the use of an enteric coating on the beadlets in the capsule. The enteric coating dissolves when the beadlets empty into the small intestine, the site of drug absorption. With buffered formulations of didanosine, administration with antacid provides protection from degradation by stomach acid.

In healthy volunteers, as well as subjects infected with HIV-1, the AUC is equivalent for didanosine administered as the didanosine-EC formulation relative to a buffered tablet formulation. The peak plasma concentration ( $C_{max}$ ) of didanosine, administered as didanosine EC, is reduced approximately 40% relative to didanosine buffered tablets. The time to the peak concentration ( $T_{max}$ ) increases from approximately 0.67 hours for didanosine buffered tablets to 2.0 hours for didanosine EC.

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

In the presence of food, the  $C_{max}$  and AUC for didanosine enteric-coated (didanosine EC) were reduced by approximately 46% and 19%, respectively, compared to the fasting state. (see **DOSAGE AND ADMINISTRATION**). Didanosine should be taken on an empty stomach.

### ***Efavirenz***

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

In HIV-1-infected patients at steady state, mean  $C_{max}$ , mean  $C_{min}$ , and mean AUC were dose proportional following 200 mg, 400 mg, and 600 mg daily doses. Time-to-peak plasma concentrations were approximately 3–5 hours and steady-state plasma

concentrations were reached in 6–10 days. In 35 patients receiving efavirenz 600 mg once daily, steady-state  $C_{\max}$  was  $12.9 \pm 3.7 \mu\text{M}$  (mean  $\pm$  SD), steady-state  $C_{\min}$  was  $5.6 \pm 3.2 \mu\text{M}$ , and the AUC was  $184 \pm 73 \mu\text{M}\cdot\text{h}$ .

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

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  $\text{AUC}_{\infty}$  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**).

***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  $^{14}\text{C}$ -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**

**ODIVIR Kit** is indicated for the treatment of HIV-1 infection, when therapy is warranted. Each kit contains once-daily doses of three commonly used antiretroviral drugs.

## DOSAGE AND ADMINISTRATION

**ODIVIR-250 Kit** is intended for patients weighing <60 kg.

**ODIVIR-400 Kit** is intended for patients weighing >60 kg.

It is important to take all the three drugs on an empty stomach before dinner, or 2 hours after dinner. The capsule should be swallowed intact.

### Dosage Adjustment

#### *Renal Impairment*

Lamivudine: Patients with impaired renal function, ie, creatinine clearance <50 mL/min require a dose adjustment.

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.

Didanosine: In adult patients with renal impairment, the dose of the didanosine enteric-coated formulation requires adjustment to compensate for the slower rate of elimination.

#### *Hepatic Impairment*

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

Efavirenz: The pharmacokinetics of efavirenz has not been adequately studied in patients with hepatic impairment [**see WARNINGS AND PRECAUTIONS**]. 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 SUSTIVA to these patients [**see WARNINGS AND PRECAUTIONS**].

Didanosine: No dose adjustment is required in patients with hepatic impairment [**see WARNINGS AND PRECAUTIONS**].

**ODIVIR Kit** is not suitable for the above categories of patients.

## CONTRAINDICATIONS

**ODIVIR Kit** is contraindicated in patients with clinically significant hypersensitivity (eg, anaphylaxis) to any of the components of the kit.

Coadministration of didanosine and allopurinol is contraindicated because systemic exposures of didanosine are increased, which may increase didanosine-associated toxicity (see **PHARMACOLOGY**).

Co-administration of didanosine and ribavirin is contraindicated because exposures of the active metabolite of didanosine (dideoxyadenosine 5'-triphosphate) are increased. Fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in patients receiving both didanosine and ribavirin.

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 2.

**Table 2: Drugs That Are Contraindicated or Not Recommended for Use with Efavirenz**

Drug Class: Drug Name	Clinical Comment
Antimigraine: ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylegonovine)	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

#### *Didanosine*

#### Established Drug Interactions

Clinical recommendations based on the results of drug interaction studies are listed in Table 3 (see **CONTRAINDICATIONS**). Pharmacokinetic results of drug interaction studies are shown in Tables 4 & 5. (see **CONTRAINDICTIONS**).

**Table 3: Established drug interactions based on studies with didanosine EC or studies with buffered formulations of didanosine and expected to occur with didanosine EC**

Drug	Effect	Clinical Comment
Ganciclovir	↑ didanosine concentration	If there is no suitable alternative to ganciclovir, then use in combination with didanosine with caution. Monitor for didanosine-associated toxicity.
Methadone	↓ didanosine concentration	If co-administration of methadone and didanosine is necessary, the recommended formulation of didanosine is <b>DINEX EC Capsules</b> . Patients should be closely monitored for adequate clinical response when <b>DINEX EC Capsules</b> are co-administered with methadone, including monitoring for changes in HIV RNA viral load. Do not co-administer methadone with didanosine pediatric powder due to significant decreases in didanosine concentrations.
Nelfinavir	No interaction 1 hour after didanosine	Administer nelfinavir 1 hour after <b>DINEX EC Capsules</b> .
Tenofovir disoproxil fumarate	↑ didanosine concentration	A dose reduction of <b>DINEX EC Capsules</b> to the dosage given below once daily and taken together with tenofovir disoproxil fumarate and a light meal (400 kcalories or less and 20% fat or less) or in the fasted state is recommended. <sup>a</sup> <ul style="list-style-type: none"> <li>• 250 mg (adults weighing at least 60 kg with creatinine clearance of at least 60 mL/min)</li> <li>• 200 mg (adults weighing less than 60 kg with creatinine clearance of at least 60 mL/min)</li> </ul> <p>Patients should be monitored for didanosine-associated toxicities and clinical response.</p>

↑ Indicates increase.

↓ Indicates decrease.

<sup>a</sup> Co-administration of didanosine with food decreases didanosine concentrations. Thus, although not studied, it is possible that co-administration with heavier meals could reduce didanosine concentrations further.

Exposure to didanosine is increased when co-administered with tenofovir disoproxil fumarate (Table 5). Increased exposure may cause or worsen didanosine-related

clinical toxicities, including pancreatitis, symptomatic hyperlactatemia/lactic acidosis, and peripheral neuropathy. Co-administration of tenofovir disoproxil fumarate with didanosine should be undertaken with caution, and patients should be monitored closely for didanosine-related toxicities and clinical response. Didanosine should be suspended if signs or symptoms of pancreatitis, symptomatic hyperlactatemia, or lactic acidosis develop (see **DOSAGE AND ADMINISTRATION; WARNINGS AND PRECAUTIONS**). Suppression of CD4 cell counts has been observed in patients receiving tenofovir disoproxil fumarate with didanosine at a dose of 400 mg daily.

### Predicted Drug Interactions

Predicted drug interactions with didanosine are listed in Table 4.

**Table 4: Predicted drug interactions with Didanosine**

Drug or Drug Class	Effect	Clinical Comment
Drugs that may cause pancreatic toxicity	↑ risk of pancreatitis	Use only with extreme caution. <sup>a</sup>
Neurotoxic drugs	↑ risk of neuropathy	Use with caution. <sup>b</sup>

↑ Indicates increase

<sup>a</sup> Only if other drugs are not available and if clearly indicated. If treatment with life-sustaining drugs that cause pancreatic toxicity is required, suspension of didanosine is recommended (see **WARNINGS AND PRECAUTIONS**).

<sup>b</sup> (See **WARNINGS AND PRECAUTIONS**)

### **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 5, 6 and 7.

**Table 5: 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-naive 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.
Protease inhibitor: Ritonavir	↑ Ritonavir <sup>a</sup> ↑ Efavirenz <sup>a</sup>	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:	↑ or ↓ Warfarin	Plasma concentrations and effects potentially

Warfarin		increased or decreased by efavirenz.
Anticonvulsants: Carbamazepine	↓ Carbamazepine <sup>a</sup> ↓ Efavirenz <sup>a</sup>	There are insufficient data to make a dose recommendation for efavirenz. Alternative anticonvulsant treatment should be used.
Phenytoin Phenobarbital	↓Anticonvulsant ↓ Efavirenz	Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.
Antidepressant: Sertraline	↓ Sertraline <sup>a</sup>	Increases in sertraline dose should be guided by clinical response.
Antifungals:  Voriconazole	↓Voriconazole <sup>a</sup>  ↑efavirenz <sup>a</sup>	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 daily using the

<p>Itraconazole</p>	<p>↓ Itraconazole<sup>a</sup> ↓ Hydroxyitraconazole<sup>a</sup></p>	<p>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>Ketoconazole</p>	<p>↓ Ketoconazole</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>Posaconazole</p>	<p>↓ Posaconazole<sup>a</sup></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 been studied in combination with efavirenz.</p>





Cyclosporine, tacrolimus, sirolimus and others metabolized by CYP3A		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.	<p><sup>a</sup> See Tables 8 and 9 for magnitude of established interactions.</p> <p><sup>b</sup> This table is not all-inclusive.</p> <p><b>Other Drugs</b> Based on the results of drug interaction studies, no dosage adjustment is recommended when efavirenz is given</p>
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.	

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, 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.

### ***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.

### **Pancreatitis**

Fatal and non-fatal pancreatitis has occurred during therapy with didanosine used alone or in combination regimens in both treatment-naïve and treatment-experienced patients,

regardless of degree of immunosuppression. Didanosine Capsules should be suspended in patients with signs or symptoms of pancreatitis. Patients treated with Didanosine Capsules in combination with stavudine, with or without hydroxyurea, may be at increased risk for pancreatitis.

When treatment with life-sustaining drugs known to cause pancreatic toxicity is required, suspension of didanosine therapy is recommended. In patients with risk factors for pancreatitis, Didanosine should be used with extreme caution and only if clearly indicated. Patients with advanced HIV-1 infection, especially the elderly, are at increased risk of pancreatitis and should be followed closely. Patients with renal impairment may be at greater risk for pancreatitis if treated without dose adjustment. The frequency of pancreatitis is dose-related. (see **UNDESIRABLE EFFECTS**)

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

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, didanosine and other antiretrovirals. A majority of these have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Fatal lactic acidosis has been reported in pregnant women who received the combination of didanosine and stavudine with other antiretroviral agents. The combination of didanosine and stavudine 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**).

Particular caution should be exercised when administering lamivudine and didanosine 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 didanosine should be suspended in any patient who develops clinical signs or symptoms with or without laboratory findings consistent with symptomatic hyperlactatemia, lactic acidosis, or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

### **Non-cirrhotic Portal Hypertension**

Postmarketing cases of non-cirrhotic portal hypertension have been reported, including cases leading to liver transplantation or death. Cases of didanosine-associated non-cirrhotic portal hypertension were confirmed by liver biopsy in patients with no evidence of viral hepatitis. Onset of signs and symptoms ranged from months to years after start of didanosine therapy. Common presenting features included elevated liver enzymes, esophageal varices, hematemesis, ascites, and splenomegaly.

Patients receiving didanosine should be monitored for early signs of portal hypertension (eg, thrombocytopenia and splenomegaly) during routine medical visits. Appropriate laboratory testing including liver enzymes, serum bilirubin, albumin, complete blood count, and international normalized ratio (INR) and ultrasonography should be considered. Didanosine should be discontinued in patients with evidence of non-cirrhotic portal hypertension.

### **Peripheral Neuropathy**

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

### **Retinal Changes and Optic Neuritis**

Retinal changes and optic neuritis have been reported in patients taking didanosine. Periodic retinal examinations should be considered for patients receiving didanosine (see **UNDESIRABLE EFFECTS**).

### **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***

Lamivudine Tablets and Oral Solution contain a higher dose of the same active ingredient (lamivudine) than Lamivudine-HBV Tablets. Lamivudine-HBV was developed for patients with chronic hepatitis B. The formulation and dosage of lamivudine in Lamivudine-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 Lamivudine-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).

### **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 efavirenz. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jiroveci* 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**

The pharmacokinetics of efavirenz has not been studied in patients with renal impairment. The doses of lamivudine and didanosine need to be adjusted for impaired renal function; hence, **ODIVIR KIT** is not suitable for this patient population (see **DOSAGE AND ADMINISTRATION**).

### **Hepatic Impairment**

It is unknown if hepatic impairment significantly affects didanosine pharmacokinetics. Therefore, these patients should be monitored closely for evidence of didanosine toxicity.

The pharmacokinetics of efavirenz has not been adequately studied in patients with hepatic impairment. Because of the extensive CYP450-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**).

No dose adjustment for lamivudine is required in patients with impaired hepatic function.

## **Pregnancy**

### ***Efavirenz***

#### *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 the other methods of contraception (eg, oral or other hormonal contraceptives). Women of childbearing potential should undergo pregnancy testing prior to the 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.

### ***Didanosine***

#### *Category B*

Reproduction studies have been performed in rats and rabbits at doses up to 12 and 14.2 times the estimated human exposure (based upon plasma levels), respectively, and have revealed no evidence of impaired fertility or harm to the fetus due to didanosine. At approximately 12 times the estimated human exposure, didanosine was slightly toxic to female rats and their pups during mid- and late-lactation. These rats showed reduced food intake and body weight gains but the physical and functional development of the offspring was not impaired and there were no major changes in the F2 generation. A study in rats showed that didanosine and/or its metabolites are transferred to the fetus through the placenta. Animal reproduction studies are not always predictive of human response.

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

Fatal lactic acidosis has been reported in pregnant women who received the combination of didanosine and stavudine 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 analogs (see **WARNINGS AND PRECAUTIONS**, Lactic Acidosis/Severe Hepatomegaly with Steatosis). **The combination of didanosine and stavudine 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 didanosine should be alert for an early diagnosis of lactic acidosis/hepatic steatosis syndrome.

### ***Lamivudine*** ***Category C***

There are no adequate and well-controlled studies of lamivudine 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.

### **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.** 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.

Although it is not known if efavirenz is secreted in human milk, efavirenz is secreted into the milk of lactating rats. A study in rats showed that following oral administration, didanosine and/or its metabolites were excreted into the milk of lactating rats. It is not known if didanosine is excreted into human milk. 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 didanosine, including those for didanosine EC, did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently than younger subjects. Didanosine is known to be substantially excreted by the kidney, 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, care should be taken in dose selection. In addition, renal function should be monitored and dosage adjustments should be made accordingly.

## UNDESIRABLE EFFECTS

### Efavirenz

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  $\geq 2\%$  of efavirenz-treated patients in two controlled clinical trials are presented in Table 6.

**Table 6: Selected Treatment-Emergent<sup>a</sup> Adverse Reactions of Moderate or Severe Intensity Reported in  $\geq 2\%$  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	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)

		weeks <sup>c</sup>				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 11 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 7.

**Table 7: Percent of Patients with One or More Selected Nervous System Symptoms<sup>a, b</sup>**

<b>Percent of Patients with:</b>	<b>Efavirenz 600 mg Once Daily (n=1008) %</b>	<b>Control Groups (n=635) %</b>
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 8 [see **WARNINGS AND PRECAUTIONS**].

**Table 8: 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 9.

**Table 9: 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 +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 <sup>b</sup>
<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>	≥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 Co-infected 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 non fasting patients. The clinical significance of these findings is unknown. (see **WARNINGS AND PRECAUTIONS**).

## **Observed During Clinical Practice**

The following adverse reactions have been identified during post approval 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.

### **Lamivudine**

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 10.

**Table 10: 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</b>	<b>Zidovudine* (n = 230)</b>

	(n = 251)	
<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 11.

**Table 11: 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 Endpoint Studies*		Clinical Endpoint Study*	
	Lamivudine plus zidovudine	Zidovudine <sup>†</sup>	Lamivudine plus current therapy	Placebo plus current therapy <sup>‡</sup>
Absolute neutrophil count (<750/mm <sup>3</sup> )	7.2%	5.4%	15%	13%
Hemoglobin (<8.0 g/dL)	2.9%	1.8%	2.2%	3.4%
Platelets (<50,000/mm <sup>3</sup> )	0.4%	1.3%	2.8%	3.8%
ALT (>5.0 x ULN)	3.7%	3.6%	3.8%	1.9%
AST (>5.0 x ULN)	1.7%	1.8%	4.0%	2.1%
Bilirubin (>2.5 x ULN)	0.8%	0.4%	ND	ND
Amylase (>2.0 x ULN)	4.2%	1.5%	2.2%	1.1%

\* The median duration on study was 12 months.

<sup>†</sup> Either zidovudine monotherapy or zidovudine in combination with zalcitabine.

<sup>‡</sup> 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.

### **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.

## Didanosine

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

Study AI454-152 was a 48-week, randomized, open-label study comparing didanosine (400 mg once daily) plus stavudine (40 mg twice daily) plus nelfinavir (750 mg three times daily) to zidovudine (300 mg) plus lamivudine (150 mg) combination tablets twice daily plus nelfinavir (750 mg three times daily) in 511 treatment-naïve patients. Selected clinical adverse reactions that occurred in combination with other antiretroviral agents are provided in Table 12.

**Table 12: Selected clinical adverse events (Study A1454-152)**

	Percentage of Patients <sup>b,c</sup>	
Adverse Reactions	Didanosine EC + Stavudine  + Nelfinavir  n = 258	Zidovudine/Lamivudine <sup>d</sup>  + Nelfinavir  n = 253

Diarrhea	57	58
Peripheral neurologic symptoms/Neuropathy	25	11
Nausea	24	36
Headache	22	17
Rash	14	12
Vomiting	14	19
Pancreatitis (see below)	Less than 1	*

<sup>a</sup> Median duration of treatment was 62 weeks in the didanosine EC + stavudine + nelfinavir group and 61 weeks in the zidovudine/lamivudine + nelfinavir group.

<sup>b</sup> Percentage based on treated patients.

<sup>c</sup> The incidences reported included all severity grades and all reactions regardless of causality.

<sup>d</sup> Zidovudine/lamivudine combination tablet.

\* This event was not observed in this study arm.

In clinical trials using a buffered formulation of didanosine, pancreatitis resulting in death was observed in one patient who received didanosine plus stavudine plus nelfinavir, one patient who received didanosine plus stavudine plus indinavir, and 2 of 68 patients who received didanosine plus stavudine plus indinavir plus hydroxyurea. In an early access program, pancreatitis resulting in death was observed in one patient who received didanosine EC plus stavudine plus hydroxyurea plus ritonavir plus indinavir plus efavirenz.

The frequency of pancreatitis is dose-related. In phase 3 studies with buffered formulations of didanosine, incidence ranged from 1% to 10% with doses higher than are currently recommended and 1% to 7% with recommended dose.

Selected laboratory abnormalities that occurred in a study of didanosine EC in combination with other antiretroviral agents are shown in Table 13 below:

**Table 13: Selected laboratory abnormalities (Study A1454-152)<sup>\*</sup>**

	Percent of Patients <sup>b</sup>	
	Didanosine EC + Stavudine + Nelfinavir	Zidovudine/Lamivudine <sup>c</sup> + Nelfinavir

Parameter	n = 258		n = 253	
	Grade 3–4 <sup>d</sup>	All Grades	Grades 3–4 <sup>d</sup>	All Grades
SGOT (AST)	5	46	5	19
SGPT (ALT)	6	44	5	22
Lipase	5	23	2	13
Bilirubin	Less than 1	9	Less than 1	3

<sup>a</sup> Median duration of treatment was 62 weeks in the didanosine EC + stavudine + nelfinavir group and 61 weeks in the zidovudine/lamivudine + nelfinavir group.

<sup>b</sup> Percentages based on treated patients.

<sup>c</sup> Zidovudine/lamivudine combination tablet.

<sup>d</sup> Greater than 5 x ULN for SGOT and SGPT, at least 2.1 x ULN for lipase, and at least 2.6 x ULN for bilirubin. (ULN = upper limit of normal)

### Observed During Clinical Practice

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

**Blood and Lymphatic System Disorders:** Anemia, leukopenia, and thrombocytopenia.

**Body as a Whole:** abdominal pain, alopecia, anaphylactoid reaction, asthenia, chills/fever, pain, and redistribution/accumulation of body fat. (see **WARNINGS AND PRECAUTIONS**).

**Digestive Disorders:** anorexia, dyspepsia, and flatulence.

**Exocrine Gland Disorders:** pancreatitis (including fatal cases) (see **WARNINGS AND PRECAUTIONS**), sialoadenitis, parotid gland enlargement, dry mouth, and dry eyes.

**Hepatobiliary Disorders:** symptomatic hyperlactatemia/lactic acidosis and hepatic steatosis(see **WARNINGS AND PRECAUTIONS**),non-cirrhotic portal hypertension(see **WARNINGS AND PRECAUTIONS**), hepatitis and liver failure.

**Metabolic Disorders:** diabetes mellitus, elevated serum alkaline phosphatase level, elevated serum amylase level, elevated serum gamma-glutamyltransferase level, elevated serum uric acid level, hypoglycemia and hyperglycemia.

**Musculoskeletal Disorders:** myalgia (with or without increases in creatine kinase), rhabdomyolysis including acute renal failure, and hemodialysis, arthralgia, and myopathy.

**Ophthalmologic Disorders:** retinal depigmentation and optic neuritis (see **WARNINGS AND PRECAUTIONS**).

### **Use with Stavudine- and Hydroxyurea-Based Regimens**

When didanosine is used in combination with other agents with similar toxicities, the incidence of these toxicities may be higher than when didanosine is used alone. Thus, patients treated with **DINEX EC Capsules** in combination with stavudine, with or without hydroxyurea, may be at increased risk for pancreatitis and hepatotoxicity, which may be fatal, and severe peripheral neuropathy (see **WARNINGS AND PRECAUTIONS**). The combination of **DINEX EC Capsules** and hydroxyurea, with or without stavudine, should be avoided.

## **OVERDOSAGE**

### **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 the removal of unabsorbed efavirenz. There is no specific antidote for an overdose with efavirenz. Since efavirenz is highly protein-bound, dialysis is unlikely to remove significant quantities from the blood.

### **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. 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.

### **Didanosine**

There is no known antidote for didanosine overdosage. In phase 1 studies, in which buffered formulations of didanosine were initially administered at doses ten times the currently recommended dose, toxicities included pancreatitis, peripheral neuropathy, diarrhea, hyperuricemia, and hepatic dysfunction. Didanosine is not dialyzable by peritoneal dialysis, although there is some clearance by hemodialysis (see **PHARMACOLOGY**).

### **PACKAGING INFORMATION**

**ODIVIR-250 Kit**.....Carton of 10 kits  
**ODIVIR-400 Kit**.....Carton of 10 kits

*Last updated: October 2010*