

DUOVIR-E KIT

WARNINGS: HEMATOLOGIC TOXICITY, MYOPATHY, LACTIC ACIDOSIS, EXACERBATIONS OF HEPATITIS B

ZIDOVUDINE, ONE OF THE TWO ACTIVE INGREDIENTS IN DUOVIR-E KIT, HAS BEEN ASSOCIATED WITH HEMATOLOGIC TOXICITY, INCLUDING NEUTROPENIA AND SEVERE ANEMIA, PARTICULARLY IN PATIENTS WITH ADVANCED HUMAN IMMUNODEFICIENCY VIRUS (HIV) DISEASE (SEE WARNINGS AND PRECAUTIONS).

PROLONGED USE OF ZIDOVUDINE HAS BEEN ASSOCIATED WITH SYMPTOMATIC MYOPATHY.(SEE WARNINGS AND PRECAUTIONS).

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

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

COMPOSITION

DUOVIR-E KIT

Each kit contains:

(A) One efavirenz tablet

Each film-coated tablet contains:

Efavirenz 600 mg

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

Each film-coated tablet contains:

Lamivudine 150 mg

Zidovudine 300 mg

DOSAGE FORMS

Efavirenz– Oral film-coated tablet

Lamivudine and Zidovudine– Oral fixed-dose combination tablet

DESCRIPTION

Each **DUOVIR-E Kit** contains three tablets – two fixed-dose combination tablets of lamivudine and zidovudine and one 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 α , β , γ or δ .

Both zidovudine 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 inhibition of reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleoside analogue. 3TC-TP is a weak inhibitor of mammalian DNA polymerases α , β and γ .

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

Efavirenz: Efavirenz (EFV) is 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 α , β , γ and δ are not inhibited by EFV.

Pharmacokinetics

Lamivudine/Zidovudine

Adults

One lamivudine/zidovudine tablet was bio-equivalent to one lamivudine tablet (150 mg) plus one zidovudine tablet (300 mg) following single-dose administration to fasting healthy subjects (n=24).

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

elimination. In humans, the only known metabolite is the trans-sulfoxide metabolite (approximately 5% of an oral dose after 12 hours).

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

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

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

* Data presented as mean ± standard deviation except where noted.

† Median [range].

‡ Children.

§ Adults.

#Approximate range.

Efavirenz

Absorption: 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 AUC_{∞} 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 P450 system to hydroxylated metabolites, with subsequent glucuronidation of these hydroxylated metabolites. These metabolites are essentially inactive against HIV-1. The *in vitro* studies suggest that 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

DUOVIR-E Kit is indicated for the treatment of HIV infection in adults.

DOSAGE AND ADMINISTRATION

Adults

Morning

One white tablet (zidovudine 300 mg and lamivudine 150 mg) to be taken in the morning.

Evening

One white tablet (zidovudine 300 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.

Dosage Adjustment

A reduction in the daily dose of zidovudine may be necessary in patients with mild to moderate impaired hepatic function or liver cirrhosis. Hence, **DUOVIR-E Kit** is not recommended for patients with impaired renal function.

DUOVIR-E Kit should also not be prescribed for patients requiring dosage adjustment such as those with reduced renal function (creatinine clearance <50 mL/min) or those experiencing dose-limiting adverse events.

CONTRAINDICATIONS

DUOVIR-E Kit is contraindicated in patients with previously demonstrated clinically significant hypersensitivity (eg, anaphylaxis, Stevens-Johnson Syndrome) to any of the components of the kit.

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 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, 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

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 Table 3.

Table 3: Established ^a and Other Potentially Significant ^b Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect on Concentration of Efavirenz or Concomitant Drug	Clinical Comment
Antiretroviral Agents		

<p>Protease inhibitor: Fosamprenavir calcium</p>	<p>↓ Amprenavir</p>	<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>
<p>Protease inhibitor: Atazanavir</p>	<p>↓ Atazanavir ^a</p>	<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 is not recommended.</p>
<p>Protease inhibitor: Indinavir</p>	<p>↓ Indinavir ^a</p>	<p>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</p>

		<p>compensate for the increased indinavir metabolism due to efavirenz. When indinavir at an increased dose (1000 mg every 8 hours) was given with efavirenz (600 mg once daily), the indinavir AUC and C_{min} were decreased on average by 33–46% and 39–57% respectively, compared to when indinavir (800 mg every 8 hours) was given alone.</p>
<p>Protease inhibitor: Lopinavir/ritonavir</p>	<p>↓ Lopinavir ^a</p>	<p>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</p>

		taken with food is recommended when used in combination with efavirenz.
Protease inhibitor: Ritonavir	↑ Ritonavir ^a ↑ Efavirenz ^a	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 ^a	Should not be used as sole protease inhibitor in combination with efavirenz.
CCR5 co-receptor antagonist : Maraviroc	↓ Maraviroc ^a	Refer to full prescribing information for maraviroc for guidance on coadministration with efavirenz.
Other Agents		
Anticoagulant: Warfarin	↑ or ↓ Warfarin	Plasma concentrations and effects potentially increased or decreased by efavirenz.
Anticonvulsants: Carbamazepine Phenytoin Phenobarbital	↓ Carbamazepine ^a ↓ Efavirenz ^a ↓ Anticonvulsant	There are insufficient data to make a dose recommendation for efavirenz. Alternative anticonvulsant treatment should be used.

	↓ Efavirenz	Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.
Antidepressant: Sertraline	↓ Sertraline ^a	Increases in sertraline dose should be guided by clinical response.
Antifungals: Voriconazole	↓ Voriconazole ^a ↑ Efavirenz ^a	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 capsule formulation. Efavirenz tablet should not be broken.

Itraconazole	↓ Itraconazole ^a ↓ Hydroxyitraconazole ^a	Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered.
Ketoconazole	↓ Ketoconazole	Drug interaction studies with efavirenz and ketoconazole have not been conducted. Efavirenz has the potential to decrease plasma concentrations of ketoconazole.
Posaconazole	↓ Posaconazole ^a	Avoid concomitant use unless the benefit outweighs the risks.
Anti-infective: Clarithromycin	↓ Clarithromycin ^a ↑ 14-OH metabolite ^a	Plasma concentrations decreased by efavirenz; clinical significance unknown. In uninfected volunteers, 46% developed rash while receiving efavirenz and clarithromycin. No dose adjustment of efavirenz is recommended when given with clarithromycin. Alternatives to clarithromycin, such as azithromycin, should be considered (see Other Drug following table). Other macrolide antibiotics, such as erythromycin, have not been studied in combination with efavirenz.
Antimycobacterial Rifampin	↓ Efavirenz ^a	Clinical significance of reduced efavirenz concentrations is unknown. Dosing

Rifabutin	↓ Rifabutin ^a	<p>recommendations for concomitant use of efavirenz and rifampin have not been established.</p> <p>Increase daily dose of rifabutin by 50%. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week</p>
<p>Calcium channel blockers: Diltiazem</p> <p>Others (eg, felodipine, nicardipine, nifedipine, verapamil)</p>	<p>↓ Diltiazem ^a ↓ Desacetyl diltiazem ^a ↓ N-monodesmethyl diltiazem ^a</p> <p>↓ Calcium channel blocker</p>	<p>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.</p> <p>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).</p>
HMG-CoA reductase inhibitors:		Plasma concentrations of atorvastatin,

<p>Atorvastatin Pravastatin Simvastatin</p>	<p>↓Atorvastatin ↓Pravastatin ↓Simvastatin</p>	<p>pravastatin and simvastatin decreased. Consult the full prescribing information for the HMG-CoA reductase inhibitor for guidance on individualizing the dose.</p>
<p>Hormonal Contraceptives: Oral Ethinyl estradiol / Norgsetimate</p> <p>Implant Etonogestrel</p>	<p>↑ active metabolites of Norgestimate ^a</p> <p>↓Etonogestrel</p>	<p>A reliable method of barrier contraception must be used in addition to hormonal contraceptives.</p> <p>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.</p> <p>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.</p>
<p>Immunosuppressants: Cyclosporine, tacrolimus, sirolimus and others</p>	<p>↓Immunosuppressant</p>	<p>Decreased exposure of the immunosuppressant</p>

<p>metabolized by CYP3A</p>		<p>may be expected due to 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>
<p>Narcotic analgesic: Methadone</p>	<p>↓ Methadone ^a</p>	<p>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.</p>

^a See Tables 4 and 5 for magnitude of established interactions.

^b 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 4 : Effect of Efavirenz on Co-administered Drug Plasma C_{max} and AUC and C_{min}

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	(mean % change)		
				C _{max} (90% CI)	AUC (90% CI)	C _{min} (90% CI)
Atazanavir	400 mg qd with a light meal d 1-20	600 mg qd with a light meal d 7-20	27	↓ 59% (49-67%)	↓ 74% (68-78%)	↓ 93% (90-95%)
	400 mg qd d 1-6, then 300 mg qd d 7-20 with ritonavir 100 mg qd and a light meal	600 mg qd 2 h after atazanavir and ritonavir d 7-20	13	↑ 14% ^a (↓ 17-↑ 58%)	↑ 39% ^a (2-88%)	↑ 48% ^a (24-76%)
	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			↔ ^b	↓ 33% ^b (26-39%)	↓ 39% ^b (24-51%)
	After afternoon dose			↔ ^b	↓ 37% ^b (26-46%)	↓ 52% ^b (47-57%)
	After evening dose			↓ 29% ^b (11-43%)	↓ 46% ^b (37-54%)	↓ 57% ^b (50-63%)
Lopinavir/ ritonavir	400/100 mg capsule q12h x 9 days	600 mg qd x 9 days	11,7 ^c	↔ ^d	↓ 19% ^d (↓ 36-↑ 3%)	↓ 39% ^d (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% ^d (28-44%)	↑ 36% ^d (28-44%)	↑ 32% ^d (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%) ^e
	After PM dose			↔	↔	↑ 24% (3-50%) ^e
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%) ^e
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% ^h	↓ 77% ^h	NA
	300 mg po q12h days 2-7	300 mg qd x 7 days	NA	↓ 36% ⁱ (21-49%)	↓ 55% ⁱ (45-62%)	NA
	400 mg po q12h days 2-7	300 mg qd x 7 days	NA	↑ 23% ⁱ (↓ 1-↑ 53%)	↓ 7% ⁱ (↓ 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 ^j
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%

^a Compared with atazanavir 400 mg q.d. alone.

^b Comparator dose of indinavir was 800 mg q8h × 10 days.

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

^d Values are for lopinavir; the pharmacokinetics of ritonavir 100 mg q12h is unaffected by concurrent efavirenz.

^e 95% CI.

^f Soft Gelatin Capsule.

^g Tenofovir disoproxil fumarate.

^h 90% CI not available

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

^j Not available because of insufficient data.

NA = not available.

Table 5: Effect of Co-administered Drug on Efavirenz Plasma C_{max} and AUC and C_{min}

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Efavirenz (mean % change)		
				C _{max} (90% CI)	AUC (90% CI)	C _{min} (90% CI)
Indinavir	800 mg q8h x 14 days	200 mg qd x 14 days	11	↔	↔	↔
Lopinavir/ ritonavir	400/100 mg q12h x 9 days	600 mg qd x 9 days	11,12 ^a	↔	↓ 16% (↓ 38-↑ 15%)	↓ 16% (↓ 42-↑ 20%)
Nelfinavir	750 mg q8h x 7 days	600 mg qd x 7 days	10	↓ 12% (↓ 32-↑ 13%) ^b	↓ 12% (↓ 35-↑ 18%) ^b	↓ 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%) ^b
Saquinavir SGC ^c	1200 mg q8h x 10 days	600 mg qd x 10 days	13	↓ 13% (5-20%)	↓ 12% (4-19%)	↓ 14% (2-24%) ^b
Tenofovir ^d	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% ^e	↑ 44% ^e	NA
	300 mg po q12h days 2-7	300 mg qd x 7 days	NA	↓ 14% ^f (7-21%)	↔ ^f	NA
	400 mg po q12h days 2-7	300 mg qd x 7 days	NA	↔ ^f	↑ 17% ^f (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%.

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

^c Soft Gelatin Capsule.

^d Tenofovir disoproxil fumarate.

^e 90% CI not available.

^f Relative to steady-state administration of efavirenz (600 mg once daily for 9 days).

NA = not available.

Lamivudine and Zidovudine

Antiretroviral Agents

Lamivudine:

Zalcitabine: Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another. Therefore, the use of **DUOVIR-EKit** in combination with zalcitabine is not recommended.

Zidovudine:

Stavudine: Concomitant use of **DUOVIR-E Kit** with stavudine should be avoided since an antagonistic relationship with zidovudine has been demonstrated *in vitro*.

Nucleoside Analogues Affecting DNA Replication

Some nucleoside analogs affecting DNA replication, such as ribavirin, antagonize the *in vitro* antiviral activity of zidovudine against HIV -1; hence, concomitant use of such drugs should be avoided.

Doxorubicin

Zidovudine: Concomitant use of **DUOVIR-E Kit** with doxorubicin should be avoided since an antagonistic relationship with zidovudine has been demonstrated in vitro.

Hematologic/Bone Marrow Suppressive/Cytotoxic Agents

Zidovudine: Coadministration of ganciclovir, interferon α 1fa, ribavirin, and other bone marrow suppressive or cytotoxic agents may increase the hematologic toxicity of zidovudine.

Interferon- and Ribavirin-Based Regimens

Lamivudine: Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-I/HCV virologic suppression) was seen when ribavirin was co administered with lamivudine in HIV -IIHCV co-infected patients, hepatic decompensation (some fatal) has occurred in HIV-IIHCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin (see **WARNINGS AND PRECAUTIONS**).

Trimethoprim/Sulfamethoxazole (TMP/SMX)

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

No drug interaction studies have been conducted using lamivudine/zidovudine tablets. However Table 6 presents drug interaction information for the individual components of lamivudine/zidovudine.

Lamivudine Plus Zidovudine: No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV -1-infected adult patients given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg q 12 hr).

Table 6: Effect of Co-administered Drugs on Lamivudine and Zidovudine AUC*

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

Drugs That May Alter Lamivudine Blood Concentrations					
Coadministered Drug and Dose	Lamivudine Dose	n	Lamivudine Concentrations		Concentration of Coadministered Drug
			AUC	Variability	
Nelfinavir 750 mg q 8 hr x 7 to 10 days	single 150 mg	11	↑AUC 10%	95% CI: 1% to 20%	↔
Trimethoprim 160 mg/ Sulfamethoxazole 800 mg daily x 5 days	single 300 mg	14	↑AUC 43%	90% CI: 32% to 55%	↔

Drugs That May Alter Zidovudine Blood Concentrations					
Coadministered Drug and Dose	Zidovudine Dose	n	Zidovudine Concentrations		Concentration of Coadministered Drug
			AUC	Variability	
Atovaquone 750 mg q 12 hr with food	200 mg q 8 hr	14	↑AUC 31%	Range 23% to 78% [†]	↔
Fluconazole 400 mg daily	200 mg q 8 hr	12	↑AUC 74%	95% CI: 54% to 98%	Not Reported
Methadone 30 to 90 mg daily	200 mg q 4 hr	9	↑AUC 43%	Range 16% to 64% [†]	↔
Nelfinavir 750 mg q 8 hr x 7 to 10 days	single 200 mg	11	↓AUC 35%	Range 28% to 41%	↔
Probenecid 500 mg q 6 hr x 2 days	2 mg/kg q 8 hr x 3 days	3	↑AUC 106%	Range 100% to 170% [†]	Not Assessed
Rifampin 600 mg daily x 14 days	200 mg q 8 hr X 14 days	8	↓AUC 47%	90% CI: 41% to 53%	Not Assessed
Ritonavir 300 mg q 6 hr x 4 days	200 mg q 8 hr x 4 days	9	↓AUC 25%	95% CI: 15% to 34%	↔
Valproic acid 250 mg or 500 mg q 8 hr x 4 days	100 mg q 8 hr x 4 days	6	↑AUC 80%	Range 64% to 130% [†]	Not Assessed

↑ = Increase; ↓ = Decrease; ↔ = no significant change; AUC = area under the concentration versus time curve; CI = confidence interval.

* This table is not all-inclusive.

[†] Estimated range of percent difference.

Ribavirin: *In vitro* data indicate that ribavirin reduces 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**).

Efavirenz Resistance

Efavirenz must not be used as a single agent to treat HIV or added on as a sole agent to a failing regimen. As with all other non-nucleoside reverse transcriptase inhibitors, resistant virus emerges rapidly when efavirenz is administered as monotherapy. The choice of new antiretroviral agent(s) 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 efavirenz/emtricitabine/ tenofovir disoproxil fumarate 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 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. Altogether 1% 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 in controlled trials 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, Psychiatric Symptoms**). 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.

Lamivudine and Zidovudine

Hematologic Toxicity/Bone Marrow Suppression

Zidovudine, a component of **DUOVIR-E Kit** Tablet, has been associated with hematologic toxicity, including neutropenia and anemia, particularly in patients with advanced HIV-1 disease. **DUOVIR-E Kit** Tablet should be used with caution

in patients who have bone marrow compromise, evidenced by granulocyte count less than 1000 cells/mm³ or hemoglobin less than 9.5 g/dL (see **UNDESIRABLE EFFECTS**).

Frequent blood counts are strongly recommended in patients with advanced HIV disease who are treated with **DUOVIR-E Kit**. For HIV-infected individuals and patients with asymptomatic or early HIV disease, periodic blood counts are recommended.

Myopathy

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

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination, including lamivudine, zidovudine, and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering lamivudine/zidovudine tablet to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with lamivudine/zidovudine tablet 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 has been seen 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 the 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 in **Lamivir - HBV Tablets**. **Lamivir - HBV**

was developed for treating chronic hepatitis B. Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients co-infected with HIV-1 and HBV.

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 HBV 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 HBV.

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 that ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogs such as lamivudine and zidovudine. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (eg, loss of HIV/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.** 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 greater than 6) (see the complete prescribing information for interferon and ribavirin).

Exacerbation of anemia has been reported in HIV-1/HCV co-infected patients receiving ribavirin and zidovudine. Co-administration of ribavirin and zidovudine is not advised.

Pancreatitis

Lamivudine/Zidovudine should be used with caution in patients with a history of pancreatitis or other significant risk factors for the development of pancreatitis. Treatment with lamivudine/zidovudine should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur.

Lamivudine , Zidovudine and Efavirenz

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 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

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

Reduction of the dosages of lamivudine and zidovudine is recommended for patients with impaired renal function. Patients with creatinine clearance <50 mL/min should not receive **DUOVIR-E Kit**.

Hepatic Impairment

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. A reduction in the daily dose of zidovudine may be necessary in patients with mild to moderate impaired hepatic function or liver cirrhosis.

Pregnancy

DUOVIR –E KIT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 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.

Lamivudine and Zidovudine (Category C): There are no adequate and well-controlled studies of lamivudine/zidovudine in pregnant women. Clinical trial data demonstrate that maternal zidovudine treatment during pregnancy reduces vertical transmission of HIV-1 infection to the fetus. Animal reproduction studies performed with lamivudine and zidovudine showed increased embryotoxicity and fetal malformations (zidovudine), and increased embryoletality (lamivudine). Lamivudine/Zidovudine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Treatment of HIV during pregnancy optimizes the health of both mother and fetus. Clinical trial data reviewed by FDA demonstrate that maternal zidovudine treatment significantly reduces vertical transmission of HIV-1 infection to the fetus (see **CLINICAL STUDIES**). Published data suggest that combination antiretroviral regimens may reduce the rate of vertical transmission even further. Pharmacokinetics of lamivudine and zidovudine in pregnant women are similar to the pharmacokinetics in nonpregnant women. No dose adjustments are needed during pregnancy.

In a clinical trial, adverse events among HIV-1-infected women were not different among untreated women and women treated with zidovudine. It is not known whether risks of adverse events associated with lamivudine are altered in pregnant women compared with other HIV-1-infected patients (see Human data below).

Human Data: Lamivudine: Lamivudine pharmacokinetics were 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. Lamivudine pharmacokinetics in pregnant women were similar to those seen in nonpregnant adults and in postpartum women. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples.

Zidovudine: A randomized, double-blind, placebo-controlled trial was conducted in HIV-1-infected pregnant women to determine the utility of zidovudine for the prevention of maternal-fetal HIV-1 transmission. Zidovudine treatment during

pregnancy reduced the rate of maternal-fetal HIV-1 transmission from 24.9% for infants born to placebo-treated mothers to 7.8% for infants born to mothers treated with zidovudine. There were no differences in pregnancy-related adverse events between the treatment groups. Congenital abnormalities occurred with similar frequency between neonates born to mothers who received zidovudine and neonates born to mothers who received placebo. The observed abnormalities included problems in embryogenesis (prior to 14 weeks) or were recognized on ultrasound before or immediately after initiation of study drug. Zidovudine pharmacokinetics were studied in a Phase 1 study of 8 women during the last trimester of pregnancy. As pregnancy progressed, there was no evidence of drug accumulation. The pharmacokinetics of zidovudine were similar to that of nonpregnant adults. Consistent with passive transmission of the drug across the placenta, zidovudine concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at delivery.

Lactation

The Centers for Disease Control and Prevention recommend that HIV-infected mothers should not breastfeed their infants to avoid risking post-natal transmission of HIV-1 infection. Although it is not known if efavirenz is secreted in human breast milk, efavirenz is secreted into the milk of lactating rats. Both zidovudine and lamivudine are excreted in human breast milk. It has been recommended that HIV-infected women do not breastfeed their infants in order to avoid transmission of HIV. Because of the potential for HIV-1 transmission, and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving **DUOVIR-E Kit**.

Although no studies of excretion in breast milk have been performed, lactation studies performed with lamivudine and zidovudine show that both drugs are excreted in human breast 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. In another study, after administration of a single dose of 200 mg zidovudine to 13 HIV-1-infected women, the mean concentration of zidovudine was similar in human milk and serum.

Pediatric Use

DUOVIR-E Kit is not indicated for use in children.

Geriatric Use

Clinical studies of Lamivudine plus zidovudine and also efavirenz did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. **DUOVIR-E KIT** is not recommended for patients with impaired renal

function (ie, creatinine clearance <50mL/min) (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**)

UNDESIRABLE EFFECTS

Zidovudine and Lamivudine

Lamivudine Plus Zidovudine Administered As Separate Formulations:

In 4 randomized, controlled trials of lamivudine 300 mg per day plus zidovudine 600 mg per day, the following selected clinical and laboratory adverse events were observed (see Tables 7 and 8).

Table 7: Selected Clinical Adverse Reactions (≥5% Frequency) in Four Controlled Clinical Trials with Lamivudine 300 mg/day and Zidovudine 600 mg/day

Adverse Reaction	Lamivudine plus Zidovudine (n=251)
Body as a Whole	
Headache	35%
Malaise and fatigue	27%
Fever or chills	10%
Digestive	
Nausea	33%
Diarrhea	18%
Nausea and vomiting	13%
Anorexia and/or decreased appetite	10%
Abdominal pain	9%
Abdominal cramps	6%
Dyspepsia	5%
Nervous System	
Neuropathy	12%
Insomnia and other sleep disorders	11%
Dizziness	10%
Depressive disorders	9%

Respiratory	
Nasal signs and symptoms	20%
Cough	18%
Skin	
Skin rashes	9%
Musculoskeletal	
Musculoskeletal pain	12%
Myalgia	8%
Arthralgia	5%

Pancreatitis was observed in 9 of the 2613 adult patients (0.3%) who received lamivudine in controlled clinical trials. (see**WARNINGS AND PRECAUTIONS**).

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

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

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

ULN = Upper limit of normal.

ANC = Absolute neutrophil count.

n = Number of patients assessed.

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

Observed During Clinical Practice:

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

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

Cardiovascular: Cardiomyopathy.

Endocrine and Metabolic: Gynecomastia, hyperglycemia.

Gastrointestinal: Oral mucosal pigmentation, stomatitis.

General: Vasculitis, weakness.

Hemic and Lymphatic: Aplastic anemia, anemia, lymphadenopathy, pure red cell aplasia, splenomegaly.

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

Hypersensitivity: Sensitization reactions (including anaphylaxis), urticaria.

Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.

Nervous: Paresthesia, peripheral neuropathy, seizures.

Respiratory: Abnormal breath sounds/wheezing.

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

Efavirenz

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

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.

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 9.

Table 9: Selected Treatment-Emergent ^a 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 ^b + ZDV/LAM (n=412) 180 weeks ^c	Efavirenz ^b + Indinavir (n=415) 102 weeks ^c	Indinavir + ZDV/LAM (n=401) 76 weeks ^c	Efavirenz ^b + Nelfinavir + NRTIs (n=64) 71.1 weeks ^c	Efavirenz + NRTIs (n=65) 70.9 weeks ^c	Nelfinavir + NRTIs (n=66) 62.7 weeks ^c
Body as a Whole						
Fatigue	8%	5%	9%	0	2%	3%
Pain	1%	2%	8%	13%	6%	17%
Central and Peripheral Nervous System						
Dizziness	9%	9%	2%	2%	6%	6%
Headache	8%	5%	3%	5%	2%	3%
Insomnia	7%	7%	2%	0	0	2%
Concentration impaired	5%	3%	<1%	0	0	0
Abnormal dreams	3%	1%	0	–	–	–

Somnolence	2%	2%	<1%	0	0	0
Anorexia	1%	<1%	<1%	0	2%	2%
Gastrointestinal						
Nausea	10%	6%	24%	3%	2%	2%
Vomiting	6%	3%	14%	–	–	–
Diarrhea	3%	5%	6%	14%	3%	9%
Dyspepsia	4%	4%	6%	0	0	2%
Abdominal pain	2%	2%	5%	3%	3%	3%
Psychiatric						
Anxiety	2%	4%	<1%	–	–	–
Depression	5%	4%	<1%	3%	0	5%
Nervousness	2%	2%	0	2%	0	2%
Skin and Appendages						
Rash ^d	11%	16%	5%	9%	5%	9%
Pruritus	<1%	1%	1%	9%	5%	9%

^a 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.

^bEfavirenz provided as 600 mg once daily.

^c Median duration of treatment.

^dIncludes 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.

ZDV = Zidovudine; LAM = Lamivudine

– = Not Specified.

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 10 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 10.

Table 10: Percent of Patients with One or More Selected Nervous System Symptoms^{a,b}

Percent of Patients with:	Efavirenz 600 mg Once Daily (n=1008) %	Control Groups (n=635) %
Symptoms of any severity	52.7	24.6
Mild symptoms ^c	33.3	15.6
Moderate symptoms ^d	17.4	7.7
Severe symptoms ^e	2.0	1.3
Treatment discontinuation as a result of symptoms	2.1	1.1
^a Includes events reported regardless of causality.		
^b Data from Study 006 and three Phase 2/3 studies.		
^c "Mild" = Symptoms which do not interfere with a patient's daily activities.		
^d "Moderate" = Symptoms which may interfere with daily activities.		
^e "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 11 (see **WARNINGS AND PRECAUTIONS**).

Table 11: Percent of Patients with Treatment-Emergent Rash^{a, b}

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

	dermatitis			
Treatment discontinuation as a result of rash	--	1.7	8.8	0.3
^a Includes events reported regardless of causality.				
^b Data from Study 006 and three Phase 2/3 studies.				
^c NCI Grading System.				

As seen in Table 11, rash is more common in pediatric patients and more often of higher grade (ie, more severe).

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

Laboratory Abnormalities

Selected Grade 3–4 laboratory abnormalities reported in $\geq 2\%$ of efavirenz-treated patients in two clinical trials are presented in Table 12.

Table 12: 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-Naïve Patients			Study ACTG 364 NRTI-Experienced, NNRTI- and Protease Inhibitor-Naïve Patients		
		Efavirenz ^a + ZDV / LAM (n=412)	Efavirenz ^a + Indinavir (n=415)	Indinavir + ZDV / LAM (n=401)	Efavirenz ^a + Nelfinavir + NRTIs (n=64)	Efavirenz ^a + NRTIs (n=65)	Nelfinavir + NRTIs (n=66)
Variable	Limit	180 weeks^b	102weeks^b	76 weeks^b	71.1 weeks^b	70.9 weeks^b	62.7 weeks^b
Chemistry							
ALT	>5 ULN ^x	5%	8%	5%	2%	6%	3%
AST	>5 ULN ^x	5%	6%	5%	6%	8%	8%

GGT ^c	>5 ULN ^x	8%	7%	3%	5%	0	5%
Amylase	>2 ULN ^x	4%	4%	1%	0	6%	2%
Glucose	>250 mg/dL	3%	3%	3%	5%	2%	3%
Triglycerides ^d	≥751 mg/dL	9%	6%	6%	11%	8%	17%
Hematology							
Neutrophils	<750/mm ³	10%	3%	5%	2%	3%	2%

^a Efavirenz provided as 600 mg once daily.

^b Median duration of treatment.

^c Isolated elevations of GGT in patients receiving efavirenz may reflect enzyme induction not associated with liver toxicity.

^d Non-fasting.

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 ≥ 240 mg/dL and ≥ 300 mg/dL were reported in 34% and 9%, respectively, of patients treated with efavirenz + zidovudine + lamivudine; 54% and 20%, respectively, of patients treated with efavirenz + indinavir; and 28% and 4%, respectively, of patients treated with indinavir + zidovudine + lamivudine. The effects of efavirenz on triglycerides and low-density lipids (LDL) 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 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, Fat Redistribution**).

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, photo-allergic dermatitis, skin discoloration, Stevens-Johnson syndrome.

Special Senses: Abnormal vision, tinnitus.

OVERDOSAGE

Lamivudine: One case of an adult ingesting 6 grams of lamivudine was reported; there were no clinical signs noted and hematologic tests remained normal. It is not known whether lamivudine can be removed by peritoneal dialysis or hemodialysis.

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

Efavirenz: Some patients accidentally taking 600 mg twice daily have reported increased nervous system symptoms. One patient experienced involuntary muscle contractions.

Treatment of overdose with efavirenz should consist of general supportive measures, including monitoring of vital signs and observation of the patient's clinical status. Administration of activated charcoal may be used to aid removal of unabsorbed efavirenz. There is no specific antidote for overdose with efavirenz. Since efavirenz is highly protein-bound, dialysis is unlikely to significantly remove drug from blood.

PACKAGING INFORMATION

DUOVIR-E Kit..... Carton containing 10 kits

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