

VIRADAY

WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS AND POST TREATMENT EXACERBATION OF HEPATITIS B

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGS, INCLUDING TENOFOVIR DISOPROXIL FUMARATE, A COMPONENT OF VIRADAY, IN COMBINATION WITH OTHER ANTIRETROVIRALS (SEE WARNINGS AND PRECAUTIONS).

VIRADAY IS NOT APPROVED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION AND THE SAFETY AND EFFICACY OF VIRADAY HAVE NOT BEEN ESTABLISHED IN PATIENTS CO-INFECTED WITH HBV AND HIV-1.

SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO HAVE DISCONTINUED EMTRICITABINE OR TENOFOVIR DISOPROXIL FUMARATE, WHICH ARE COMPONENTS OF VIRADAY. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO ARE COINFECTED WITH HIV-1 AND HBV AND DISCONTINUE VIRADAY. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS AND PRECAUTIONS).

COMPOSITION

VIRADAY

Each film-coated tablet contains:

Efavirenz	600 mg
Emtricitabine	200 mg
Tenofovir disoproxil fumarate	300 mg
Equivalent to Tenofovir disoproxil	245 mg

DOSAGE FORM

Oral, fixed-dose tablet

DESCRIPTION

VIRADAY is a fixed-dose combination tablet containing efavirenz, emtricitabine and tenofovir disoproxil fumarate (tenofovir DF).

PHARMACOLOGY

Pharmacodynamics

Efavirenz

Efavirenz is a non-nucleoside reverse transcriptase (RT) inhibitor of HIV-1. Efavirenz activity is mediated predominantly by the 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 efavirenz.

Emtricitabine

Emtricitabine, a synthetic nucleoside analog of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 RT by competing with the natural substrate, deoxycytidine 5'-triphosphate, and by being incorporated into nascent viral DNA, which results in chain termination. Emtricitabine 5'-triphosphate is a weak inhibitor of mammalian DNA polymerase α , β , ϵ and mitochondrial DNA polymerase, γ .

Tenofovir DF

Tenofovir DF is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir DF requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 RT by competing with the natural substrate, deoxyadenosine 5'-triphosphate, and after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases, α and β , and mitochondrial DNA polymerase, γ .

Pharmacokinetics in Adults

One **VIRADAY** is bioequivalent to one efavirenz tablet (600 mg) plus one emtricitabine capsule (200 mg) plus one tenofovir DF tablet (300 mg) following single-dose administration to fasting healthy subjects (N=45).

Efavirenz

In HIV-1-infected subjects, time-to-peak plasma concentrations were approximately 3–5 hours and steady-state plasma concentrations were reached in 6–10 days. In 35 HIV-1 infected subjects receiving efavirenz 600 mg once daily, steady-state C_{max} was $12.9 \pm 3.7 \mu\text{M}$ (mean \pm SD), C_{min} was $5.6 \pm 3.2 \mu\text{M}$, and AUC was $184 \pm 73 \mu\text{M}\cdot\text{hr}$. Efavirenz is highly bound (approximately 99.5–99.75%) to human plasma proteins, predominantly albumin. Following administration of ^{14}C -labeled efavirenz, 14–34% of the dose was

recovered in the urine (mostly as metabolites) and 16–61% was recovered in feces (mostly as parent drug). *In vitro* studies suggest 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. Efavirenz has a terminal half-life of 52–76 hours after single doses and 40–55 hours after multiple doses.

Emtricitabine

Following oral administration, emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1–2 hours post-dose. Following multiple dose oral administration of emtricitabine to 20 HIV-1-infected subjects, the steady-state plasma emtricitabine C_{max} was $1.8 \pm 0.7 \mu\text{g/mL}$ (mean \pm SD) and the AUC over a 24-hour dosing interval was $10.0 \pm 3.1 \mu\text{g}\cdot\text{hr/mL}$. The mean steady-state plasma trough concentration at 24 hours post-dose was $0.09\mu\text{g/mL}$. The mean absolute bioavailability of emtricitabine was 93%. *In vitro* binding of emtricitabine to human plasma proteins is <4% and is independent of concentration over the range of 0.02-200 $\mu\text{g/mL}$. Following administration of radiolabeled emtricitabine, approximately 86% is recovered in the urine and 13% is recovered as metabolites. The metabolites of emtricitabine include 3'-sulfoxide diastereomers and their glucuronic acid conjugate. Emtricitabine is eliminated by a combination of glomerular filtration and active tubular secretion with a renal clearance in adults with normal renal function of $213 \pm 89 \text{ ml/min}$ (mean \pm SD). Following a single oral dose, the plasma emtricitabine half-life is approximately 10 hours.

Tenofovir DF

Following oral administration of a single 300 mg dose of tenofovir DF to HIV-1- infected subjects in the fasted state, maximum serum concentrations (C_{max}) were achieved in $1.0 \pm 0.4 \text{ hrs}$ (mean \pm SD) and C_{max} and AUC values were $296 \pm 90 \text{ ng/mL}$ and $2287 \pm 685 \text{ ng}\cdot\text{hr/mL}$, respectively. The oral bioavailability of tenofovir from tenofovir DF in fasted subjects is approximately 25%. *In vitro* binding of tenofovir to human plasma proteins is <0.7% and is independent of concentration over the range of 0.01 - 25 $\mu\text{g/mL}$. Approximately 70–80% of the intravenous dose of tenofovir is recovered as unchanged drug in the urine. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion; in adults with normal renal function of $243 \pm 33 \text{ mL/min}$ (mean \pm SD). Following a single oral dose of tenofovir DF, the terminal elimination half-life of tenofovir is approximately 17 hours.

Effects of Food on Oral Absorption

VIRADAY have not been evaluated in the presence of food. Administration of efavirenz tablets with a high-fat meal increased the mean AUC and C_{max} of efavirenz by 28% and 79%, respectively, compared to administration in the fasted state. Compared to fasted administration, dosing of tenofovir DF and emtricitabine in combination with either a high-fat meal or a light meal increased the mean AUC and C_{max} of tenofovir by 35% and 15%, respectively, without affecting emtricitabine exposures (see **DOSAGE AND ADMINISTRATION**).

Special Populations

Race

Efavirenz

The pharmacokinetics of efavirenz in HIV-1 infected subjects appears to be similar among the racial groups studied.

Emtricitabine

No pharmacokinetic differences due to race have been identified following the administration of emtricitabine.

Tenofovir DF

There were insufficient numbers from racial and ethnic groups other than Caucasian to adequately determine the potential pharmacokinetic differences among these populations following the administration of tenofovir DF.

Gender

Efavirenz, Emtricitabine, and Tenofovir DF: Efavirenz, emtricitabine, and tenofovir DF pharmacokinetics are similar in male and female patients.

Pediatric and Geriatric Patients

Pharmacokinetic studies of tenofovir DF have not been performed in pediatric patients (<18 years). Efavirenz has not been studied in pediatric subjects below 3 years of age or who weigh less than 13 kg. Emtricitabine has been studied in pediatric subjects from 3 months to 17 years of age. **VIRADAY** is not recommended for pediatric administration. Pharmacokinetics of efavirenz, emtricitabine and tenofovir DF have not been fully evaluated in the elderly (>65 years of age).

Patients with Impaired Renal Function

Efavirenz

The pharmacokinetics of efavirenz has not been studied in subjects 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.

Emtricitabine and Tenofovir DF

The pharmacokinetics of emtricitabine and tenofovir DF are altered in patients with renal impairment. In subjects with creatinine clearance <50 mL/min, C_{max} and $AUC_{0-\infty}$ of emtricitabine and tenofovir were increased (see **WARNINGS AND PRECAUTIONS**).

Patients with Hepatic Impairment

Efavirenz

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

Emtricitabine

The pharmacokinetics of emtricitabine have not been studied in subjects with hepatic impairment; however, emtricitabine is not significantly metabolized by liver enzymes, so the impact of liver impairment should be limited.

Tenofovir DF

The pharmacokinetics of tenofovir, following a 300 mg dose of tenofovir DF, has been studied in non-HIV-1-infected subjects with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir DF pharmacokinetics in subjects with hepatic impairment compared with unimpaired subjects.

INDICATIONS

VIRADAY is indicated for use alone as a complete regimen or in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults.

DOSAGE AND ADMINISTRATION

Adults

The dose of **VIRADAY** is one tablet once daily taken on an empty stomach. Dosing at bedtime may improve the tolerability of nervous system symptoms.

Pediatrics

VIRADAY is not recommended for use in patients <18 years of age.

Renal Impairment

Because **VIRADAY** is a fixed-dose combination, it should not be prescribed for patients requiring dosage adjustment such as those with moderate or severe renal impairment (creatinine clearance <50 mL/min).

CONTRAINDICATIONS

Hypersensitivity

VIRADAY is contraindicated in patients with previously demonstrated clinically significant hypersensitivity (e.g., Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to efavirenz, a component of **VIRADAY**.

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 **VIRADAY** are listed in Table 1.

Table 1: Drugs that are contraindicated or not recommended for use with VIRADAY

Drug Class: Drug Name	Clinical Comment
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Antifungal Voriconazole	Efavirenz significantly decreases voriconazole plasma concentrations, and co-administration may decrease the therapeutic effectiveness of voriconazole. Also, voriconazole significantly increases efavirenz plasma concentrations, which may increase the risk of efavirenz-associated side effects. Because VIRADAY is a fixed-dose combination product, the dose of efavirenz cannot be altered.
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 (NNRTIs).

WARNINGS AND PRECAUTIONS

Drug Interactions

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**).

Efavirenz

Efavirenz has been shown *in vivo* to induce CYP3A4. Other compounds that are substrates of CYP3A4 may have decreased plasma concentrations when co-administered with efavirenz. *In vitro* studies have demonstrated that efavirenz inhibits CYP2C9, 2C19, and 3A4 isozymes in the range of observed efavirenz plasma concentrations. Coadministration of efavirenz with drugs primarily metabolized by these isozymes may result in altered plasma concentrations of the coadministered drug. Therefore, appropriate dose adjustments may be necessary for these drugs. Drugs which induce CYP3A4 activity (eg, phenobarbital, rifampin, rifabutin) would be expected to increase the clearance of efavirenz, resulting in lowered plasma concentrations.

Emtricitabine and Tenofovir DF

Since emtricitabine and tenofovir are primarily eliminated by the kidneys, coadministration of **VIRADAY** with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of emtricitabine, tenofovir DF, and/or other renally eliminated drugs. Some examples include, but are not limited to, acyclovir, adefovir dipivoxil, cidofovir, ganciclovir, valacyclovir, and valganciclovir.

Coadministration of tenofovir DF and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse reactions. Didanosine should be discontinued in patients who develop didanosine-associated adverse reactions (for didanosine dosing adjustment recommendations, see Table 2). Suppression of CD4+ cell counts has been observed in patients receiving tenofovir DF with didanosine 400 mg daily.

Lopinavir/ritonavir has been shown to increase tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving lopinavir/ritonavir with **VIRADAY** should be monitored for tenofovir DF-associated adverse reactions. **VIRADAY** should be discontinued in patients who develop tenofovir DF-associated adverse reactions (see Table 2).

Co-administration of atazanavir with **VIRADAY** is not recommended since co-administration of atazanavir with either efavirenz or tenofovir DF has been shown to decrease plasma concentrations of atazanavir. Also, atazanavir has been shown to increase tenofovir concentrations. There are insufficient data to support dosing recommendations for atazanavir or atazanavir/ritonavir in combination with **VIRADAY** (see Table 2).

Efavirenz, Emtricitabine and Tenofovir DF

Other important drug interaction information for **VIRADAY** is summarized in Table 1 and Table 2. The drug interactions described are based on studies conducted with efavirenz, emtricitabine or tenofovir DF as individual agents, or are potential drug interactions; no drug interaction studies have been conducted using **VIRADAY**. The tables include potentially significant interactions, but are not all inclusive.

Table 2: Established and other potentially significant^a drug interactions: Alteration in dose or regimen may be recommended based on drug interaction studies or predicted interaction

Concomitant Drug Class: Drug Name	Effect	Clinical Comment
<i>Antiretroviral Agents</i>		
Protease inhibitor: Atazanavir	↓ atazanavir concentration ↑ tenofovir DF	Co-administration of atazanavir with VIRADAY is not recommended. Co-administration of atazanavir with

	concentration	either efavirenz or tenofovir DF decreases plasma concentrations of atazanavir. The combined effect of efavirenz plus tenofovir DF on atazanavir plasma concentrations is not known. Also, atazanavir has been shown to increase tenofovir DF concentrations. There are insufficient data to support dosing recommendations for atazanavir or atazanavir/ritonavir in combination with VIRADAY .
Protease inhibitor: Fosamprenavir calcium	↓ amprenavir concentration	<i>Fosamprenavir (unboosted):</i> Appropriate doses of fosamprenavir and VIRADAY with respect to safety and efficacy have not been established. <i>Fosamprenavir/ritonavir:</i> An additional 100 mg/day (300 mg total) of ritonavir is recommended when VIRADAY is administered with fosamprenavir/ritonavir once daily. No change in the ritonavir dose is required when VIRADAY is administered with fosamprenavir plus ritonavir twice daily.
Protease inhibitor: Indinavir	↓ indinavir concentration	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.
Protease inhibitor: Lopinavir/ritonavir	↓ lopinavir concentration ↑ tenofovir concentration	A dose increase of lopinavir/ritonavir to 600/150 mg (3 tablets) 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). Patients should be monitored for tenofovir DF-associated adverse reactions. VIRADAY should be discontinued

		in patients who develop tenofovir DF-associated adverse reactions.
Protease inhibitor: Ritonavir	↑ ritonavir concentration ↑ efavirenz concentration	When ritonavir 500 mg every 12 hours was coadministered with efavirenz 600 mg once daily, 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 VIRADAY is used in combination with ritonavir.
Protease inhibitor: Saquinavir	↓ saquinavir concentration	Should not be used as sole protease inhibitor in combination with VIRADAY .
CCR5 co-receptor antagonist: Maraviroc	Maraviroc concentration	Efavirenz decreases plasma concentrations of maraviroc. Refer to the full prescribing information for maraviroc for guidance on coadministration with VIRADAY .
NRTI: Didanosine	↑ didanosine concentration	Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis and neuropathy. In adults weighing >60 kg, the didanosine dose should be reduced to 250 mg if coadministered with VIRADAY. Data are not available to recommend a dose adjustment of didanosine for patients weighing <60 kg. Coadministration of VIRADAY and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse reactions. For additional information, please consult the didanosine prescribing information.

Other Agents		
Anticoagulant Warfarin	↑ or ↓ warfarin concentration	Plasma concentrations and effects potentially increased or decreased by efavirenz.
Anticonvulsants Carbamazepine Phenytoin Phenobarbital	↓ carbamazepine ↓ efavirenz ↓ anticonvulsant ↓ efavirenz concentration	There are insufficient data to make a dose recommendation for VIRADAY . Alternative anticonvulsant treatment should be used. Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.
Antidepressant Sertraline	↓ sertraline concentration	Increases in sertraline dose should be guided by clinical response.
Antifungals Itraconazole Ketoconazole Posaconazole	↓ itraconazole concentration ↓ hydroxyitraconazole concentration ↓ ketoconazole concentration ↓ Posaconazole concentration	Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered. Drug interaction studies with efavirenz/emtricitabine/tenofovir DF and ketoconazole have not been conducted. Efavirenz plasma concentrations of ketoconazole. Avoid concomitant use unless the benefit outweighs the risks.
Anti-infective Clarithromycin	↓ clarithromycin concentration ↑ 14-OH metabolite concentration	Clinical significance unknown. In uninfected volunteers, 46% developed rash while receiving efavirenz and clarithromycin. No dose adjustment of VIRADAY is recommended when given with clarithromycin. Alternatives to clarithromycin, such as azithromycin, should be considered. Other macrolide antibiotics, such as

		erythromycin, have not been studied in combination with efavirenz/emtricitabine/tenofovir DF.
Antimycobacterial Rifampin	↓ efavirenz concentration	Clinical significance of reduced efavirenz concentration is unknown. Dosing recommendations for concomitant use of VIRADAY and rifampin have not been established.
Rifabutin	↓ rifabutin concentration	Increase daily dose of rifabutin by 50%. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week
Calcium channel blocker Diltiazem Others (eg, felodipine, nifedipine, verapamil)	↓ diltiazem concentration ↓ desacetyl diltiazem concentration ↓ N-monodesmethyl diltiazem concentration ↓ calcium channel blocker	Diltiazem dose adjustments should be guided by clinical response (refer to the prescribing information for diltiazem). No dose adjustment of VIRADAY is necessary when administered with diltiazem. No data are available on the potential interactions of efavirenz with other calcium channel blockers that are substrates of the CYP3A. The potential exists for reduction in plasma concentrations of the calcium channel blocker. Dose adjustments should be guided by clinical response (refer to the prescribing information for the calcium channel blocker).
HMG-CoA reductase inhibitors Atorvastatin Pravastatin	↓ atorvastatin concentration ↓ pravastatin concentration ↓ simvastatin	Plasma concentrations of atorvastatin, pravastatin and simvastatin decreased. Consult the complete prescribing information for the HMG-CoA reductase inhibitor for guidance on individualizing the dose.

Simvastatin	concentration	
Immunosuppressants: Cyclosporine, tacrolimus, sirolimus, and others metabolized by CYP3A	↓Immunosuppressant	Decreased exposure of the immunosuppressant may be expected due to CYP3A induction by efavirenz. 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 VIRADAY .
Narcotic analgesic Methadone	↓ methadone concentration	Co-administration of efavirenz in HIV-1-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.
Hormonal contraceptives: Oral Ethinyl estradiol/Norgestimate	↓Active metabolites of norgestimate	A reliable method of barrier contraception must be used in addition to hormonal contraceptives. Efavirenz had no effect on ethinyl estradiol concentrations, but progestin levels (norelgestromin and levonorgestrel) were markedly decreased. No effect of ethinyl estradiol/norgestimate on efavirenz plasma concentrations was observed.
Implant Etonogestrel	↓Etonogestrel	A reliable method of barrier contraception must be used in addition to hormonal contraceptives. The interaction between etonogestrel and efavirenz has not

		been studied. Decreased exposure of etonogestrel may be expected. There have been postmarketing reports of contraceptive failure with etonogestrel in efavirenz-exposed patients.

^a This table is not all-inclusive.

Efavirenz Assay Interference

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. For more information, please consult the efavirenz prescribing information.

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 including tenofovir DF, a component of **VIRADAY**, in combination with 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 nucleoside analogs 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 **VIRADAY** 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 Coinfected with HIV-1 and HBV

It is recommended that all patients with HIV-1 be tested for the presence of chronic HBV before initiating antiretroviral therapy. **VIRADAY** is not approved for the treatment of chronic HBV infection, and the safety and efficacy of **VIRADAY** have not been established in patients coinfecting with HBV and HIV-1. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfecting with HBV and HIV-1 and have discontinued emtricitabine and tenofovir DF, two of the components of **VIRADAY**. In some patients infected with HBV and treated with emtricitabine, the exacerbations of hepatitis B were associated with liver decompensation and liver failure. Patients who are coinfecting with HIV-1 and HBV should be closely monitored with both clinical and laboratory follow up for at least several months after stopping treatment with **VIRADAY**. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

VIRADAY should not be administered with adefovir dipivoxil. (see **DRUG INTERACTIONS**).

Coadministration with Related Products

Related drugs not for co-administration with **VIRADAY** include emtricitabine, tenofovir DF, emtricitabine/tenofovir DF, and efavirenz, which contain the same active components as **VIRADAY**. Due to similarities between emtricitabine and lamivudine, **VIRADAY** should not be coadministered with drugs containing lamivudine, including lamivudine/zidovudine, or lamivudine, abacavir sulfate/lamivudine, or abacavir sulfate/lamivudine/zidovudine.

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 subjects who received efavirenz or control regimens, respectively, were severe depression (2.4%, 0.9%), suicidal ideation (0.7%, 0.3%), nonfatal suicide attempts (0.5%, 0%), aggressive behavior (0.4%, 0.5%), paranoid reactions (0.4%, 0.3%), and manic reactions (0.2%, 0.3%). When psychiatric symptoms similar to those noted above were combined and evaluated as a group in a multifactorial analysis of data from Study AI266006 (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 subjects. One percent of efavirenz-treated subjects 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

Fifty-three percent (531/1008) of subjects 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 dizziness (28.1% of the 1008 subjects), insomnia (16.3%), impaired concentration (8.3%), somnolence (7.0%), abnormal dreams (6.2%), and hallucinations (1.2%). Other

reported symptoms were euphoria, confusion, agitation, amnesia, stupor, abnormal thinking, and depersonalization. The majority of these symptoms were mild-moderate (50.7%); symptoms were severe in 2.0% of patients. Overall, 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 subjects 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 subjects were generally similar to those in the indinavir-containing control arm.

Patients receiving **VIRADAY** should be alerted to the potential for additive central nervous system effects when **VIRADAY** 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.

New Onset or Worsening Renal Impairment

Emtricitabine and tenofovir are principally eliminated by the kidney; however, efavirenz is not. Since **VIRADAY** is a combination product and the dose of the individual components cannot be altered, patients with creatinine clearance <50 mL/min should not receive **VIRADAY**.

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir DF (see **UNDESIRABLE EFFECTS**).

It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with **VIRADAY**. Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment, including patients who have previously experienced renal events while receiving adefovir dipivoxil.

VIRADAY should be avoided with concurrent or recent use of a nephrotoxic agent.

Rash

In controlled clinical trials, 26% (266/1008) of subjects treated with 600 mg efavirenz experienced new-onset skin rash compared with 17% (111/635) of subjects treated in control groups. Rash associated with blistering, moist desquamation, or ulceration occurred in 0.9% (9/1008) of subjects treated with efavirenz. The incidence of Grade 4 rash (eg, erythema multiforme, Stevens-Johnson syndrome) in subjects 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 subjects 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). **VIRADAY** can be reinitiated in patients interrupting therapy because of rash. **VIRADAY** 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.

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

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 also **WARNINGS AND PRECAUTIONS**). 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 **VIRADAY** needs to be weighed against the unknown risks of significant liver toxicity (See **UNDESIRABLE EFFECTS**).

Decreases in Bone Mineral Density

Bone mineral density (BMD) monitoring should be considered for HIV-1-infected subjects who have a history of pathologic bone fracture or are at risk for osteopenia. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected, then appropriate consultation should be obtained.

In a 144-week study of treatment-naïve subjects receiving tenofovir DF, decreases in BMD were seen at the lumbar spine and hip in both arms of the study. At week 144,

there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in subjects receiving tenofovir DF + lamivudine + efavirenz compared with subjects receiving stavudine + lamivudine + efavirenz. Changes in BMD at the hip were similar between the two treatment groups. In both groups, the majority of the reduction in BMD occurred in the first 24–48 weeks of the study and this reduction was sustained through 144 weeks. Twenty-eight percent of tenofovir DF-treated subjects vs 21% of the comparator subjects lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 subjects in the tenofovir DF group and 6 patients in the comparator group. Tenofovir DF was associated with significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide, and urinary N-telopeptide), suggesting increased bone turnover. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in subjects receiving tenofovir DF. The effects of tenofovir DF-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. For additional information, consult the tenofovir DF prescribing information.

Cases of osteomalacia (associated with proximal renal tubulopathy and which may contribute to fractures) have been reported in association with the use of tenofovir DF (see **UNDESIRABLE EFFECTS**).

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**).

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including the components of **VIRADAY**. During the initial phase of combination antiretroviral treatment, patients whose immune system responds to such treatment 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.

Pregnancy

Pregnancy Category D

Efavirenz may cause fetal harm when administered during the first trimester to a pregnant woman. Pregnancy should be avoided in women receiving **VIRADAY**. 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 **VIRADAY** is recommended. Women of childbearing potential should undergo pregnancy testing before initiation of **VIRADAY**. 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 of **VIRADAY** in pregnant women. **VIRADAY** should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus, such as in pregnant women without other therapeutic options.

Lactation

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1. Studies in rats have demonstrated that both tenofovir and efavirenz are secreted in milk. It is not known whether efavirenz, tenofovir or emtricitabine are excreted in human milk. Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving VIRADAY.**

Pediatric Use

VIRADAY is not recommended for patients less than 18 years of age because it is a fixed-dose combination tablet containing a component, tenofovir DF, for which safety and efficacy have not been established in this age group.

Geriatric Use

Clinical studies of efavirenz, emtricitabine, or tenofovir DF 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 the elderly patients should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Hepatic Impairment

The pharmacokinetics of efavirenz has not been adequately studied in subjects with hepatic impairment. Because of the extensive cytochrome P450-mediated metabolism of efavirenz and limited clinical experience in patients with hepatic impairment, caution should be exercised in administering **VIRADAY** to these patients (see **WARNINGS AND PRECAUTIONS**).

Renal Impairment

Because **VIRADAY** is a fixed-dose combination, it should not be prescribed for patients requiring dosage adjustment such as those with moderate or severe renal impairment (creatinine clearance <50 mL/min) (see **WARNINGS AND PRECAUTIONS**).

UNDESIRABLE EFFECTS

Efavirenz, Emtricitabine and Tenofovir DF: The following are the adverse reactions:

- Lactic acidosis/Severe hepatomegaly with steatosis (see **BOXED WARNING; WARNINGS AND PRECAUTIONS**).
- Severe acute exacerbations of hepatitis B (see **BOXED WARNING; WARNINGS AND PRECAUTIONS, Patients with HIV and HBV Co-infection**).
- Psychiatric Symptoms (see **WARNINGS AND PRECAUTIONS**).
- Nervous system Symptoms (see **WARNINGS AND PRECAUTIONS**).
- New Onset or worsening renal impairment (see **WARNINGS AND PRECAUTIONS**).
- Rash (see **WARNINGS AND PRECAUTIONS**).
- Decreases in bone mineral density (see **WARNINGS AND PRECAUTIONS**).
- Immune reconstitution syndrome (see **WARNINGS AND PRECAUTIONS**).
- Drug interactions (see **CONTRAINDICATIONS; WARNINGS AND PRECAUTIONS, Drug Interactions**).

For additional safety information about efavirenz, emtricitabine, or tenofovir DF in combination with other antiretroviral agents, consult the prescribing information for these products.

Adverse Reactions from Clinical Trials Experience

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.

Study 934

Study 934 was an open-label, active-controlled study in which 511 antiretroviral-naïve patients received either emtricitabine + tenofovir DF administered in combination with efavirenz (N = 257) or zidovudine/lamivudine administered in combination with efavirenz (N = 254).

The most common adverse reactions (incidence $\geq 10\%$, any severity) occurring in Study 934 included diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia,

abnormal dreams, and rash. Adverse reactions observed in Study 934 were generally consistent with those seen in previous studies of the individual components (Table 3).

Table 3: Selected treatment-emergent adverse reactions^a (Grades 2–4) reported in ≥5% in any treatment group in Study 934 (0–144 weeks)

	FTC + TDF + EFV^b (N = 257)	AZT/3TC + EFV (N = 254)
Gastrointestinal Disorder		
Diarrhea	9%	5%
Nausea	9%	7%
Vomiting	2%	5%
General Disorders and Administration Site Condition		
Fatigue	9%	8%
Infections and Infestations		
Sinusitis	8%	4%
Upper respiratory tract infections	8%	5%
Nasopharyngitis	5%	3%
Nervous System Disorders		
Headache	6%	5%
Dizziness	8%	7%
Psychiatric Disorders		
Anxiety	5%	4%
Depression	9%	7%
Insomnia	5%	7%
Skin and Subcutaneous Tissue Disorders		
Rash event ^c	7%	9%

^a Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.

^b From weeks 96 to 144 of the study, subjects received emtricitabine/tenofovir DF administered in combination with efavirenz in place of emtricitabine plus tenofovir DF with efavirenz.

^c Rash event includes rash, exfoliative rash, rash generalized, rash macular, rash maculo-papular, rash pruritic, and rash vesicular.

Study 073

In Study 073, subjects with stable, virologic suppression on antiretroviral therapy and no history of virologic failure were randomized to receive efavirenz, emtricitabine, or tenofovir DF or to stay on their baseline regimen. The adverse reactions observed in Study 073 were generally consistent with those seen in Study 934 and those seen with

the individual components of efavirenz, emtricitabine, or tenofovir DF when each was administered in combination with other antiretroviral agents.

Efavirenz, Emtricitabine, or Tenofovir Disoproxil Fumarate

In addition to the adverse reactions in Study 934 and Study 073 the following adverse reactions were observed in clinical trials of efavirenz, emtricitabine, or tenofovir DF in combination with other antiretroviral agents.

Efavirenz

The most significant adverse reactions observed in subjects treated with efavirenz are nervous system symptoms (See **WARNINGS AND PRECAUTIONS**, psychiatric symptoms (See **WARNINGS AND PRECAUTIONS** and rash (See **WARNINGS AND PRECAUTIONS**).

Selected adverse reactions of moderate-severe intensity observed in $\geq 2\%$ of efavirenz treated subjects in two controlled clinical trials included pain, impaired concentration, abnormal dreams, somnolence, anorexia, dyspepsia, abdominal pain, nervousness, and pruritus.

Pancreatitis has also 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 subjects treated with efavirenz 600 mg than in control subjects.

Emtricitabine and Tenofovir Disoproxil Fumarate

Adverse reactions that occurred in at least 5% of treatment-experienced or treatment-naive subjects receiving emtricitabine or tenofovir DF with other antiretroviral agents in clinical trials include arthralgia, increased cough, dyspepsia, fever, myalgia, pain, abdominal pain, back pain, paresthesia, peripheral neuropathy (including peripheral neuritis and neuropathy), pneumonia, rhinitis and rash event (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash and allergic reaction). Skin discoloration has been reported with higher frequency among emtricitabine-treated subjects; it was manifested by hyperpigmentation on the palms and/or soles and was generally mild and asymptomatic. The mechanism and clinical significance are unknown.

Laboratory Abnormalities

Efavirenz, Emtricitabine and Tenofovir Disoproxil Fumarate

Laboratory abnormalities observed in Study 934 were generally consistent with those seen in previous studies (Table 4).

Table 4: Significant Laboratory Abnormalities Reported in $\geq 1\%$ of Subjects in Either Treatment Group in Study 934 (0–144 Weeks)

			FTC + TDF + EFV^a (N = 257)	AZT/3TC + EFV (N = 254)
Any	\geq Grade	3	30%	26%

laboratory abnormality		
Fasting cholesterol (>240 mg/mL)	22%	24%
Creatine kinase (M: >990 U/L) (F: >845 U/L)	9%	7%
Serum amylase (>175 U/L)	8%	4%
Alkaline phosphatase (>550 U/L)	1%	0%
AST (M: >180 U/L) (F: >170 U/L)	3%	3%
ALT (M: >215 U/L) (F: >170 U/L)	2%	3%
Hemoglobin (<8.0 mg/dL)	0%	4%
Hyperglycemia (>250 mg/dL)	2%	1%
Hematuria (>75 RBC/HPF)	3%	2%
Glycosuria (≥3+)	<1%	1%
Neutrophils (<750/mm ³)	3%	5%
Fasting triglycerides (>750 mg/dL)	4%	2%

^a From weeks 96 to 144 of the study, subjects received emtricitabine/tenofovir DF administered in combination with efavirenz in place of emtricitabine + tenofovir DF with efavirenz.

Laboratory abnormalities observed in Study 073 were generally consistent with those in Study 934.

In addition to the laboratory abnormalities described for Study 934 (Table 4), Grade 3/4 elevations of bilirubin (>2.5 x ULN), pancreatic amylase (>2.0 x ULN), serum glucose (<40 or >250 mg/dL), and serum lipase (>2.0 x ULN) occurred in up to 3% of subjects treated with emtricitabine or tenofovir DF with other antiretroviral agents in clinical trials.

Hepatic Events

In Study 934, 19 subjects treated with efavirenz, emtricitabine, and tenofovir DF and 20 subjects treated with efavirenz and fixed-dose zidovudine/lamivudine were hepatitis B surface antigen or hepatitis C antibody positive. Among these coinfecting subjects, one subject (1/19) in the efavirenz, emtricitabine and tenofovir DF arm had elevations in transaminases to greater than five times ULN through 144 weeks. In the fixed-dose zidovudine/lamivudine arm, two subjects (2/20) had elevations in transaminases to

greater than five times ULN through 144 weeks. No HBV and/or HCV coinfecting subject discontinued from the study due to hepatobiliary disorders (see **WARNINGS AND PRECAUTIONS**).

Observed During Clinical Practice

The following adverse reactions given below have been identified during post-approval use of efavirenz, emtricitabine, or tenofovir DF. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Efavirenz

Cardiac disorders: Palpitations

Ear and labyrinth disorders: Tinnitus

Endocrine disorders: Gynecomastia

Eye disorders: Abnormal vision

Gastrointestinal disorders: Constipation, malabsorption

General disorders and administration site conditions: Asthenia

Hepatobiliary disorders: 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.

Immune system disorders: Allergic reactions

Metabolism and nutrition disorders: Redistribution/accumulation of body fat (see **WARNINGS AND PRECAUTIONS**), hypercholesterolemia, hypertriglyceridemia

Musculoskeletal and connective tissue disorders: Arthralgia, myalgia, myopathy

Nervous system disorders: Abnormal coordination, ataxia, cerebellar coordination and balance disturbances, convulsions, hypoesthesia, paresthesia, neuropathy, tremor

Psychiatric disorders: Aggressive reactions, agitation, delusions, emotional lability, mania, neurosis, paranoia, psychosis, suicide

Respiratory, thoracic and mediastinal disorders: Dyspnea

Skin and subcutaneous tissue disorders: Flushing, erythema multiforme, photoallergic dermatitis, Stevens-Johnson syndrome

Emtricitabine

No postmarketing adverse reactions have been identified for inclusion in this section.

Tenofovir DF

Immune system disorders: Allergic reaction, including angioedema

Metabolism and nutrition disorders Lactic acidosis, hypokalemia, Hypophosphatemia

Respiratory, thoracic, and mediastinal disorders: Dyspnea

Gastrointestinal disorders: Abdominal pain, increased amylase, pancreatitis

Hepatobiliary disorders: hepatic steatosis, hepatitis, Increased liver enzymes (most commonly AST, ALT, gamma GT),

Skin and subcutaneous tissue disorders: Rash

Musculoskeletal and connective tissue disorders: rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy

Renal and Urinary disorders: acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, , interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria

General disorders and administration site conditions: Asthenia

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia, hypokalemia, muscular weakness, myopathy, hypophosphatemia.

OVERDOSAGE

If overdose occurs, the patient should be monitored for evidence of toxicity, including monitoring of vital signs and observation of the patient's clinical status; standard supportive treatment should then be applied as necessary. Administration of activated charcoal may be used to aid the removal of unabsorbed efavirenz. Hemodialysis can remove both emtricitabine and tenofovir DF (refer to detailed information below), but is unlikely to significantly remove efavirenz from the blood.

Efavirenz

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

Emtricitabine

Limited clinical experience is available at doses higher than the therapeutic dose of emtricitabine. In one clinical pharmacology study, single doses of emtricitabine 1200 mg were administered to 11 patients. No severe adverse reactions were reported.

Hemodialysis treatment removes approximately 30% of the emtricitabine dose over a 3-hour dialysis period starting within 1.5 hours of emtricitabine dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min). It is not known whether emtricitabine can be removed by peritoneal dialysis.

Tenofovir DF

Limited clinical experience at doses higher than the therapeutic dose of tenofovir DF 300 mg is available. In one study, 600 mg tenofovir DF was administered to 8 subjects orally for 28 days, and no severe adverse reactions were reported. The effects of higher doses are not known.

Tenofovir DF is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of tenofovir DF, a 4-hour hemodialysis session removed approximately 10% of the administered tenofovir DF dose.

PACKAGING INFORMATION

VIRADAY.....Container of 30 tablets

Last updated: October 2010