

VIRADAY Tablets (Efavirenz + Emtricitabine + Tenofovir disoproxil fumarate)

Black Box Warning

Post Treatment Exacerbation of Hepatitis B

Severe acute exacerbations of hepatitis B virus (HBV) have been reported in patients who are coinfecting with HIV-1 and HBV and have discontinued products containing emtricitabine (FTC) and/or tenofovir disoproxil fumarate (TDF), which are components of VIRADAY. Closely monitor hepatic function with both clinical and laboratory follow-up for at least several months in patients who are co-infected 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, alpha, beta, gamma and delta are not inhibited by efavirenz.

Cardiac Electrophysiology

The effect of efavirenz on the QTc interval was evaluated in an open-label, positive and placebo-controlled, fixed single sequence 3-period, 3-treatment crossover QT study in 58 healthy subjects enriched for CYP2B6 polymorphisms. The mean C_{max} of efavirenz in subjects with CYP2B6 *6/*6 genotype following the administration of 600 mg daily dose for 14 days was 2.25-fold the mean C_{max} observed in subjects with CYP2B6 *1/*1 genotype. A positive relationship between

efavirenz concentration and QTc prolongation was observed. Based on the concentration-QTc relationship, the mean QTc prolongation and its upper bound 90% confidence interval are 8.7 msec and 11.3 msec in subjects with CYP2B6*6/*6 genotype following the administration of 600 mg daily dose for 14 days (see WARNINGS AND PRECAUTIONS).

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 alpha, beta, epsilon and mitochondrial DNA polymerase gamma.

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 alpha, beta, and mitochondrial DNA polymerase gamma.

► Pharmacokinetics in adults

One efavirenz/emtricitabine/tenofovir disoproxil fumarate tablet 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 $1.8 \pm 0.7 \mu\text{g}/\text{mL}$ (mean \pm SD) and the AUC over a 24-hour dosing interval was $10.0 \pm 3.1 \mu\text{g}\cdot\text{hr}/\text{mL}$. The mean steady-state plasma trough concentration at 24 hours post-dose was $0.09 \mu\text{g}/\text{mL}$. The mean absolute bioavailability of emtricitabine was 93%. Less than 4% of emtricitabine binds to human plasma proteins *in vitro* and the binding is independent of concentration over the range of 0.02-200 $\mu\text{g}/\text{mL}$. 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 $213 \pm 89 \text{ ml}/\text{min}$ (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 ng/mL and 2287 ± 685 ng•hr/mL, respectively. The oral bioavailability of tenofovir from tenofovir DF in fasted subjects is approximately 25%. Less than 0.7% of tenofovir binds to human plasma proteins *in vitro* and the binding is independent of concentration over the range of 0.01 - 25 µg/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 with a renal clearance in adults with normal renal function of 243 ± 33 mL/min (mean \pm SD). Following a single oral dose, the terminal elimination half-life of tenofovir is approximately 17 hours.

Effects of Food on Oral absorption

Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate 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 appear 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 pharmacokinetics are similar in male and female subjects.

Geriatric Patients

Pharmacokinetics of efavirenz, emtricitabine and tenofovir have not been fully evaluated in the elderly (65 years of age and older) (see WARNINGS AND PRECAUTIONS).

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 subjects with renal impairment. In subjects with creatinine clearance below 50 mL/min, C_{max} and $AUC_{0-\infty}$ of emtricitabine and tenofovir were increased (see WARNINGS AND PRECAUTIONS).

Patients with Hepatic Impairment

Efavirenz: A multiple-dose trial showed no significant effect on efavirenz pharmacokinetics in subjects with mild hepatic impairment (Child-Pugh Class A) compared with controls. There were insufficient data to determine whether moderate or severe hepatic impairment (Child-Pugh Class B or C) affects efavirenz pharmacokinetics. (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

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 the treatment of HIV-1 infection in adults only.

Dosage And Administration

► Testing prior to Initiation and During Treatment with VIRADAY

Prior to or when initiating VIRADAY, test patients for hepatitis B virus infection (see WARNINGS AND PRECAUTIONS).

Prior to initiation and during use of VIRADAY, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus (see WARNINGS AND PRECAUTIONS).

Monitor hepatic function prior to and during treatment with VIRADAY (see WARNINGS AND PRECAUTIONS).

Perform pregnancy testing before initiation of VIRADAY in adolescents and adults of childbearing potential (see WARNINGS AND PRECAUTIONS, USE IN SPECIFIC POPULATIONS).

► Recommended Dosage for Adults

VIRADAY is a three-drug fixed-dose combination product containing 600 mg of efavirenz (EFV), 200 mg of emtricitabine (FTC), and 300 mg of tenofovir disoproxil fumarate (TDF). The recommended dosage of VIRADAY in adults is one tablet once daily taken orally on an empty stomach. Dosing at bedtime may improve the tolerability of nervous system symptoms.

Not Recommended in Patients with Moderate or Severe Renal Impairment

VIRADAY is not recommended in patients with moderate or severe renal impairment (estimated creatinine clearance below 50 mL/min) (see WARNINGS AND PRECAUTIONS, USE IN SPECIFIC POPULATIONS).

► Not Recommended in Patients with Moderate to Severe Hepatic Impairment

VIRADAY is not recommended in patients with moderate to severe hepatic impairment (Child Pugh B or C) (see WARNINGS AND PRECAUTIONS, USE IN SPECIFIC POPULATIONS).

► Dosage Adjustment with Rifampin

If VIRADAY is co-administered with rifampin to patients weighing 50 kg or more, take one tablet of VIRADAY once daily followed by one additional 200 mg per day of efavirenz (see WARNING AND PRECAUTIONS-Drug Interactions).

Contraindications

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 (see WARNINGS AND PRECAUTIONS).

VIRADAY is contraindicated to be coadministered with voriconazole or elbasvir/grazoprevir (see WARNINGS AND PRECAUTIONS-Drug Interactions)

Warnings And Precautions

► Drug Interactions

Efavirenz

Efavirenz has been shown *in vivo* to induce CYP3A and CYP2B6. Other compounds that are substrates of CYP3A or CYP2B6 may have decreased plasma concentrations when co-administered with efavirenz.

Drugs which induce CYP3A activity (eg, phenobarbital, rifampin, rifabutin) would be expected to increase the clearance of efavirenz, resulting in lowered plasma concentrations (see DOSAGE AND ADMINISTRATION).

There is limited information available on the potential for a pharmacodynamic interaction between efavirenz and drugs that prolong the QTc interval. QTc prolongation has been observed with the use of efavirenz (see PHARMACOLOGY).

Consider alternatives to efavirenz/emtricitabine/tenofovir disoproxil fumarate when co-administered with a drug with a known risk of Torsade de Pointes.

Drugs Affecting Renal Function

Emtricitabine and tenofovir are primarily eliminated by the kidneys. Co-administration of efavirenz/emtricitabine/tenofovir disoproxil fumarate with drugs that are eliminated by active tubular secretion may increase concentrations of emtricitabine, tenofovir, and/or the co-administered drugs. Some examples include, but are not limited to, acyclovir, adefovir dipivoxil, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs (see WARNINGS AND PRECAUTIONS). Drugs that decrease renal function may increase concentrations of FTC and/or tenofovir.

Established and Potentially Significant Interactions

Other important drug interaction information for efavirenz/emtricitabine/tenofovir disoproxil fumarate is summarized in Table 1. The drug interactions described are based on trials conducted with efavirenz/emtricitabine/tenofovir disoproxil fumarate, the components of efavirenz/emtricitabine/tenofovir disoproxil fumarate (efavirenz, emtricitabine or tenofovir DF) as individual agents, or are potential drug interactions

Table 1: Established and potentially significant drug interactions

Concomitant Drug Class: Drug Name	Effect	Clinical Comment
<i>HIV antiviral agents</i>		
Protease inhibitor: atazanavir	↓ atazanavir ↑ tenofovir	Co-administration of atazanavir with efavirenz/emtricitabine/tenofovir disoproxil fumarate is not recommended. The combined effect of efavirenz plus tenofovir DF on atazanavir plasma concentrations is not known. There are insufficient data to support dosing recommendations for atazanavir or atazanavir/ritonavir in combination with efavirenz/emtricitabine/tenofovir disoproxil fumarate.

Protease inhibitor: Ritonavir	↑ ritonavir ↑ efavirenz	When ritonavir 500 mg every 12 hours 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/emtricitabine/tenofovir disoproxil fumarate is used in combination with ritonavir.
Protease inhibitor: Saquinavir	↓ saquinavir	Appropriate doses of the combination of efavirenz and saquinavir/ritonavir with respect to safety and efficacy have not been established.
CCR5 co-receptor antagonist: Maraviroc	↓ maraviroc	Refer to the full prescribing information for maraviroc for guidance on co-administration with efavirenz/emtricitabine/tenofovir disoproxil fumarate.
NRTI: didanosine	↑ didanosine	Patients receiving efavirenz/emtricitabine/tenofovir disoproxil fumarate and didanosine should be monitored closely for didanosine-associated adverse reactions. Discontinue didanosine in patients who develop didanosine-associated adverse reactions. Higher didanosine concentrations could potentiate didanosine associated adverse reactions, including pancreatitis, and neuropathy. Suppression of CD4+ cell counts has been observed in patients receiving tenofovir DF with didanosine 400 mg daily. In patients weighing greater than 60 kg, reduce the didanosine dose to 250 mg when it is coadministered with efavirenz/emtricitabine/tenofovir disoproxil fumarate. In patients weighing less than 60 kg, reduce the didanosine dose to 200 mg when it is coadministered with efavirenz/emtricitabine/tenofovir disoproxil fumarate. When coadministered, efavirenz/emtricitabine/tenofovir disoproxil fumarate and didanosine may be taken under fasted conditions or with a light meal (less than 400 kcal, 20% fat).
NNRTI: Other NNRTIs	↑ or ↓ efavirenz and/or NNRTI	Combining two NNRTIs has not been shown to be beneficial. efavirenz/emtricitabine/tenofovir disoproxil fumarate contains efavirenz and should not be co-administered with other NNRTIs.

Integrase strand transfer inhibitor: Raltegravir	↓ raltegravir	The clinical significance of this interaction has not been directly assessed.
<i>Hepatitis C antiviral agents</i>		
Protease inhibitor: Boceprevir	↓ boceprevir	Plasma trough concentrations of boceprevir were decreased when boceprevir was co-administered with efavirenz, which may result in loss of therapeutic effect. The combination should be avoided.
elbasvir/grazoprevir	↓ elbasvir ↓ grazoprevir	Coadministration of efavirenz/emtricitabine/tenofovir disoproxil fumarate with elbasvir/grazoprevir is contraindicated (see CONTRAINDICATIONS) because it may lead to loss of virologic response to elbasvir/grazoprevir.
glecaprevir/pibrentasvir	↓ pibrentasvir ↓ glecaprevir	Coadministration of efavirenz/emtricitabine/tenofovir disoproxil fumarate is not recommended because it may lead to reduced therapeutic effect of pibrentasvir/glecaprevir.
Protease inhibitor: Simeprevir	↓ simeprevir ↔ efavirenz	Concomitant administration of simeprevir and efavirenz result in loss of therapeutic effect of simeprevir.
ledipasvir/sofosbuvir	↑ tenofovir	Patients receiving efavirenz/emtricitabine/tenofovir disoproxil fumarate and ledipasvir/sofosbuvir concomitantly should be monitored for adverse reactions associated with tenofovir DF.
sofosbuvir/velpatasvir sofosbuvir/velpatasvir/ voxilaprevir	↑ tenofovir ↓ velpatasvir ↓ voxilaprevir	Coadministration of efavirenz-containing regimens and sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/ voxilaprevir is not recommended.
<i>Other agents</i>		
Anticoagulant Warfarin	↑ or ↓ warfarin	Plasma concentrations and effects potentially increased or decreased by efavirenz.

Anticonvulsants Carbamazepine	↓ carbamazepine ↓ efavirenz	There are insufficient data to make a dose recommendation for efavirenz/emtricitabine/tenofovir disoproxil fumarate. Alternative anticonvulsant treatment should be used.
Phenytoin Phenobarbital	↓ anticonvulsant ↓ efavirenz	Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.
Antidepressant Bupropion	↓ bupropion	The effect of efavirenz on bupropion exposure is thought to be due to the induction of bupropion metabolism. Increases in bupropion dosage should be guided by clinical response, but the maximum recommended dose of bupropion should not be exceeded.
Sertraline	↓ sertraline	Increases in sertraline dose should be guided by clinical response.
Antifungals Itraconazole	↓ itraconazole ↓ hydroxy- itraconazole	Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered.
Ketoconazole	↓ ketoconazole	Drug interaction trials with efavirenz/emtricitabine/tenofovir DF and ketoconazole have not been conducted. Efavirenz has the potential to decrease plasma concentrations of ketoconazole.
Posaconazole	↓ posaconazole	Avoid concomitant use unless the benefit outweighs the risks.
Voriconazole	↓ voriconazole ↑ efavirenz	Coadministration of efavirenz/emtricitabine/tenofovir DF with voriconazole is contraindicated (see CONTRAINDICATIONS) because it may lead to reduced therapeutic effect of voriconazole and increased risk of EFV-associated adverse reactions
Anti-infective Clarithromycin	↓ clarithromycin ↑ 14-OH metabolite	Consider alternatives to macrolide antibiotics because of the risk of QT interval prolongation

Antimycobacterial Rifabutin	↓ rifabutin	Increase daily dose of rifabutin by 50%. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week.
Rifampin	↓ efavirenz	If efavirenz/emtricitabine/tenofovir disoproxil fumarate tablet is co-administered with rifampin to patients weighing 50 kg or more, an additional 200 mg/day of efavirenz is recommended.
Antimalarials artemether/ lumefantrine	↓ artemether ↓ dihydro- artemisinin ↓ lumefantrine	Consider alternatives to artemether/ lumefantrine because of the risk of QT interval prolongation.
atovaquone/proguanil	↓ atovaquone ↓ proguanil	Concomitant administration of atovaquone/proguanil with efavirenz/ emtricitabine/tenofovir disoproxil fumarate is not recommended
Calcium channel Blocker: diltiazem	↓ diltiazem ↓ desacetyl diltiazem ↓ N-monode- -methyl diltiazem	Diltiazem dose adjustments should be guided by clinical response (refer to the prescribing information for diltiazem). No dose adjustment of efavirenz/emtricitabine/tenofovir disoproxil fumarate is necessary when administered with diltiazem.
Others (eg, felodipine, nicardipine, nifedipine, verapamil)	↓ calcium channel blocker	No data are available on the potential interactions of efavirenz with other calcium channel blockers that are substrates of the 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 full prescribing information for the calcium channel blocker).
HMG-CoA reductase inhibitors Atorvastatin Pravastatin Simvastatin	↓ atorvastatin ↓ pravastatin ↓ simvastatin	Plasma concentrations of atorvastatin, pravastatin and simvastatin decreased with efavirenz. Consult the full prescribing information for the HMG-CoA reductase inhibitor for guidance on individualizing the dose.

<p>Hormonal contraceptives: Oral: Ethinyl estradiol/Norgestimate</p> <p>Implant Etonogestrel</p>	<p>↓ active metabolites of norgestimate</p> <p>↓ etonogestrel</p>	<p>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.</p> <p>A reliable method of barrier contraception must be used in addition to hormonal contraceptives. 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 metabolized by CYP3A</p>	<p>↓ immuno-suppressant</p>	<p>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 efavirenz/emtricitabine/ tenofovir disoproxil fumarate.</p>
<p>Narcotic analgesic Methadone</p>	<p>↓ methadone</p>	<p>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.</p>

^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 reported with some screening assays in uninfected and HIV-infected subjects receiving efavirenz. Confirmation of positive screening tests for cannabinoids by a more specific method is recommended

► Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs including tenofovir DF, a component of efavirenz/emtricitabine/tenofovir disoproxil fumarate, in combination with other antiretrovirals. Treatment with efavirenz/emtricitabine/tenofovir disoproxil fumarate 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).

► Severe Acute Exacerbation of Hepatitis B in Patients Coinfected with HIV-1 and HBV

All patients should be tested for the presence of chronic HBV before or when initiating antiretroviral therapy (see DOSAGE AND ADMINISTRATION). Severe acute exacerbations of hepatitis B (e.g., liver decompensation and liver failure) have been reported in patients who are coinfecting with HBV and HIV-1 and have discontinued emtricitabine or tenofovir DF, two of the components of efavirenz/emtricitabine/tenofovir disoproxil fumarate. 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 efavirenz/emtricitabine/tenofovir disoproxil fumarate. If appropriate, initiation of antihepatitis B therapy may be warranted, especially in patients with advanced liver disease or cirrhosis, since posttreatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure.

► Risk of Adverse Reactions or Loss of Virologic Response Due to Drug

Interactions

The concomitant use of efavirenz/emtricitabine/tenofovir disoproxil fumarate and other drugs may result in potentially significant drug interactions (see CONTRAINDICATIONS and WARNING AND PRECAUTIONS - Drug Interactions), some of which may lead to:

- Loss of therapeutic effect of concomitant drug or efavirenz/emtricitabine/tenofovir disoproxil fumarate and possible development of resistance.

- Possible clinically significant adverse reaction from greater exposures of efavirenz/emtricitabine/tenofovir disoproxil fumarate or concomitant drug.

QTc prolongation has been observed with the use of efavirenz (see WARNING AND PRECAUTIONS- Drug Interactions and PHARMACOLOGY). Consider alternatives to efavirenz/emtricitabine/tenofovir disoproxil fumarate when co-administered with a drug with a known risk of Torsade de Pointes or when administered to patients at higher risk of Torsade de Pointes.

See Table 1 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during efavirenz/emtricitabine/tenofovir disoproxil fumarate therapy and review concomitant medications during efavirenz/emtricitabine/tenofovir disoproxil fumarate therapy (see DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS and WARNING AND PRECAUTIONS - Drug Interactions).

► Psychiatric Symptoms

Serious psychiatric adverse experiences have been reported in patients treated with efavirenz a component of efavirenz/emtricitabine/tenofovir disoproxil fumarate. In controlled trials of 1008 subjects treated with regimens containing efavirenz for a mean of 2.1 years and 635 subjects 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) (006, NCT00002410), a Phase 3 randomized, open-label trial of EFV-containing regimens versus controls in 1,266 subjects (median follow-up 180 weeks, 102 weeks, and 76 weeks for subjects treated with EFV + zidovudine + lamivudine, EFV + indinavir, and indinavir + zidovudine + lamivudine, respectively), treatment with EFV 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 trial 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 trial 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. Postmarketing cases of catatonia have also been reported and may be associated with increased EFV exposure. 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 subjects 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 subjects. Overall, 2.1% of subjects 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 subjects 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 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 efavirenz/emtricitabine/tenofovir disoproxil fumarate should be alerted to the potential for additive central nervous system effects when efavirenz/emtricitabine/tenofovir disoproxil fumarate 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. 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 a component of efavirenz/emtricitabine/tenofovir disoproxil fumarate (see UNDESIRABLE EFFECTS).

Prior to initiation and during use of efavirenz/emtricitabine/tenofovir disoproxil fumarate, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus. efavirenz/emtricitabine/tenofovir disoproxil fumarate is not recommended in patients with moderate or severe renal impairment (estimated creatinine clearance below 50 mL/min).

Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate should be avoided with concurrent or recent use of a nephrotoxic

agent (e.g., high-dose or multiple non-steroidal anti-inflammatory drugs) (see WARNING AND PRECAUTION-Drug Interactions). Cases of acute renal failure after initiation of high dose or multiple NSAIDs have been reported in HIV-infected patients with risk factors for renal dysfunction who appeared stable on tenofovir DF. Some patients required hospitalization and renal replacement therapy. Alternatives to NSAIDs should be considered, if needed, in patients at risk for renal dysfunction.

Persistent or worsening bone pain, pain in extremities, fractures and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function in at-risk patients. Discontinue efavirenz/emtricitabine/tenofovir disoproxil fumarate in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

► Embryo-Fetal Toxicity

Efavirenz may cause fetal harm when administered during the first trimester of pregnancy. Advise adults and adolescents of childbearing potential who are receiving efavirenz/emtricitabine/tenofovir disoproxil fumarate to avoid pregnancy while receiving efavirenz/emtricitabine/tenofovir disoproxil fumarate and for 12 weeks after discontinuation (see DOSAGE AND ADMINISTRATION, USE IN SPECIFIC POPULATIONS).

► 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 trials 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). Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate can be reinitiated in patients interrupting therapy because of rash. Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate 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. For patients who have had a life-threatening cutaneous reaction (eg, Stevens-Johnson syndrome), alternative therapy should be considered (see CONTRAINDICATIONS).

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.

Rash was reported in 59 of 182 pediatric subjects (32%) treated with efavirenz (see UNDESIRABLE EFFECTS). Two pediatric subjects experienced Grade 3 rash (confluent rash with fever, generalized rash), and four subjects had Grade 4 rash (erythema multiforme). The median time to onset of rash in pediatric subjects was 28 days (range 3-1642 days). Prophylaxis with appropriate antihistamines before initiating therapy with efavirenz/emtricitabine/tenofovir disoproxil fumarate in pediatric patients should be considered.

► Hepatotoxicity

Postmarketing cases of hepatitis, including fulminant hepatitis progressing to liver failure requiring transplantation or resulting in death, have been reported in patients treated with EFV, a component of efavirenz/emtricitabine/tenofovir disoproxil fumarate. Reports have included patients with underlying hepatic disease, including coinfection with hepatitis B or C, and patients without preexisting hepatic disease or other identifiable risk factors (see WARNINGS AND

PRECAUTIONS).

Efavirenz/emtricitabine/tenofovir disoproxil fumarate is not recommended for patients with moderate or severe hepatic impairment. Careful monitoring is recommended for patients with mild hepatic impairment receiving efavirenz/emtricitabine/tenofovir disoproxil fumarate (see UNDESIRABLE EFFECTS and USE IN SPECIFIC POPULATIONS). Monitoring of liver enzymes before and during treatment is recommended for all patients (see DOSAGE AND ADMINISTRATION). Consider discontinuing efavirenz/emtricitabine/tenofovir disoproxil fumarate in patients with persistent elevations of serum transaminases to greater than five times the upper limit of the normal range. Discontinue efavirenz/emtricitabine/tenofovir disoproxil fumarate if elevation of serum transaminases is accompanied by clinical signs or symptoms of hepatitis or hepatic decompensation (see UNDESIRABLE EFFECTS).

► Bone Loss and Mineralization Defects

Bone Mineral Density

In clinical trials in HIV-1 infected adults, tenofovir DF (a component of efavirenz/emtricitabine/tenofovir disoproxil fumarate) was associated with slightly greater decreases in bone mineral density (BMD) and increases in biochemical markers of bone metabolism, suggesting increased bone turnover relative to comparators. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in subjects receiving tenofovir DF.

Clinical trials evaluating tenofovir DF in pediatric and adolescent subjects were conducted. Under normal circumstances, BMD increases rapidly in pediatric patients. In HIV-1 infected subjects aged 2 years to less than 18 years, bone effects were similar to those observed in adult subjects and suggest increased bone turnover. Total body BMD gain was less in the tenofovir DF treated HIV-1 infected pediatric subjects as compared to the control groups. Similar trends were observed in chronic hepatitis B infected adolescent subjects aged 12 years to less than 18 years. In all pediatric trials, skeletal growth (height) appeared to be unaffected. The effects of tenofovir DF-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. Assessment of BMD should be considered for adult and pediatric patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. 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.

Mineralization Defects

Cases of osteomalacia associated with proximal renal tubulopathy, manifested as bone pain or pain in extremities and which may contribute to fractures, have been reported in association with the use of tenofovir DF (see UNDESIRABLE EFFECTS). Arthralgias and muscle pain or weakness have also been reported in cases of proximal renal tubulopathy. Hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving products containing tenofovir DF (see WARNINGS AND PRECAUTIONS).

► Convulsions

Convulsions have been observed in adult and pediatric 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 WARNING AND PRECAUTIONS-Drug Interactions).

► Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including the components of efavirenz/emtricitabine/tenofovir disoproxil fumarate. During the initial phase of combination

antiretroviral treatment, patients whose immune system may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia, and tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of 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 including efavirenz. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

► Pregnancy

Risk Summary

There are retrospective case reports of neural tube defects in infants whose mothers were exposed to efavirenz-containing regimens in the first trimester of pregnancy. Prospective pregnancy data from the APR are not sufficient to adequately assess this risk. Although a causal relationship has not been established between exposure to efavirenz in the first trimester and neural tube defects, similar malformations have been observed in studies conducted in monkeys at doses similar to the human dose. In addition, fetal and embryonic toxicities occurred in rats at a dose 10 times less than the human exposure at the recommended clinical human dose (RHD) of efavirenz. Because of the potential risk of neural tube defects, efavirenz is not recommended for use in the first trimester of pregnancy. Avoid pregnancy while receiving efavirenz/emtricitabine/tenofovir disoproxil fumarate and for 12 weeks after discontinuation. Advise pregnant patients of the potential risk to a fetus.

Available data from the APR show no increase in the overall risk of major birth defects for efavirenz, emtricitabine, or tenofovir DF compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP).

The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15- 20%. The background risk of major birth defects and miscarriage for the indicated population is unknown. The APR uses the MACDP as the U.S. reference population for birth defects in the general population. The MACDP evaluates mothers and infants from a limited geographic area and does not include outcomes for births that occurred at less than 20 weeks' gestation.

In animal reproduction studies, no adverse developmental effects were observed when FTC and TDF were administered separately at doses/exposures ≥ 60 (FTC), ≥ 14 (TDF) and 2.7 (tenofovir) times those at the RHD of efavirenz/emtricitabine/tenofovir disoproxil fumarate.

Data

Human Data

Efavirenz: There are retrospective postmarketing reports of findings consistent with neural tube defects, including meningocele, all in infants of mothers exposed to Efavirenz-containing regimens in the first trimester.

Based on prospective reports to the APR of 1,217 exposures to efavirenz-containing regimens during pregnancy resulting in live births (including over 1,023 live births exposed in the first trimester and 194 exposed in the second/third trimester), there was no increase in overall birth defects with efavirenz compared with the background birth defect of 2.7% in the U.S. reference population of the MACDP. The prevalence of birth defects in live births was 2.3% (95% CI: 1.5% to 3.5%) with first trimester exposure to efavirenz-containing regimens, and 1.5% (95% CI: 0.3% to 4.5%) with the

second/third trimester exposure to efavirenz-containing regimens. One of these prospectively reported defects with first-trimester exposure was a neural tube defect. A single case of anophthalmia with first-trimester exposure to efavirenz has also been prospectively reported. This case also included severe oblique facial clefts and amniotic banding, which have a known association with anophthalmia.

Emtricitabine: Based on prospective reports from the APR of 4,005 exposures to emtricitabine containing regimens during pregnancy resulting in live births (including 2,785 exposed in the first trimester and 1,220 exposed in the second/third trimester), there was no increase in overall major birth defects with emtricitabine compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of birth defects in live births was 2.4% (95% CI: 1.9% to 3.1%) with first trimester exposure to emtricitabine-containing regimens and 2.3% (95% CI: 1.5% to 3.3%) with the second/third trimester exposure to emtricitabine-containing regimens.

Tenofovir DF: Based on prospective reports from the APR of 5,105 exposures to tenofovir DF containing regimens during pregnancy resulting in live births (including 3,535 exposed in the first trimester and 1,570 exposed in the second/third trimester), there was no increase in overall major birth defects with tenofovir DF compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of birth defects in live births was 2.3% (95% CI: 1.8% to 2.9%) with first trimester exposure to tenofovir DF-containing regimens, and 2.2% (95% CI: 1.6% to 3.1%) with the second/third trimester exposure to tenofovir DF-containing regimens.

Animal Data

Efavirenz: Effects of efavirenz on embryo-fetal development have been studied in three nonclinical species (cynomolgus monkeys, rats, and rabbits). In monkeys, efavirenz 60 mg/kg/day was administered to pregnant females throughout pregnancy (gestation days 20 through 150). The maternal systemic drug exposures (AUC) were 1.3 times the exposure in humans at the recommended clinical dose (600 mg/day), with fetal umbilical venous drug concentrations approximately 0.7 times the maternal values. Three fetuses of 20 fetuses/infants had one or more malformations; there were no malformed fetuses or infants from placebo-treated mothers. The malformations that occurred in these three monkey fetuses included anencephaly and unilateral anophthalmia in one fetus, microphthalmia in a second, and cleft palate in the third. There was no NOAEL (no observable adverse effect level) established for this study because only one dosage was evaluated. In rats, efavirenz was administered either during organogenesis (gestation days 7 to 18) or from gestation day 7 through lactation day 21 at 50, 100, or 200 mg/kg/day. Administration of 200 mg/kg/day in rats was associated with increase in the incidence of early resorptions; and doses 100 mg/kg/day and greater were associated with early neonatal mortality. The AUC at the NOAEL (50 mg/kg/day) in this rat study was 0.1 times that in humans at the recommended clinical dose. Drug concentrations in the milk on lactation day 10 were approximately 8 times higher than those in maternal plasma. In pregnant rabbits, efavirenz was neither embryo lethal nor teratogenic when administered at doses of 25, 50, and 75 mg/kg/day over the period of organogenesis (gestation days 6 through 18). The AUC at the NOAEL (75 mg/kg/day) in rabbits was 0.4 times that in humans at the recommended clinical dose.

Emtricitabine: Emtricitabine was administered orally to pregnant mice (at 0, 250, 500, or 1,000 mg/kg/day), and rabbits (at 0, 100, 300, or 1,000 mg/kg/day) through organogenesis (on gestation days 6 through 15, and 7 through 19, respectively). No significant toxicological effects were observed in embryo-fetal toxicity studies performed with emtricitabine in mice at exposures (AUC) approximately 60 times higher and in rabbits at approximately 120 times higher than human exposures at the RHD. In a pre/postnatal development study in mice, emtricitabine was administered orally at doses up to 1000 mg/kg/day; no significant adverse effects directly related to drug were observed in the offspring exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately 60 times higher than human exposures at the RHD.

Tenofovir DF: Tenofovir DF was administered orally to pregnant rats (at 0, 50, 150, or 450 mg/kg/day) and rabbits (at 0, 30, 100, or 300 mg/kg/day) through organogenesis (on gestation days 7 through 17, and 6 through 18, respectively). No significant toxicological effects were observed in embryo-fetal toxicity studies performed with tenofovir DF in rats at

doses up to 14 times the RHD based on body surface area comparisons and in rabbits at doses up to 19 times the RHD based on body surface area comparisons. In a pre/postnatal development study in rats, TDF was administered orally through lactation at doses up to 600 mg/kg/day; no adverse effects were observed in the offspring at tenofovir exposures of approximately 2.7 times higher than human exposures at the RHD.

▶ Lactation

Risk Summary

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.

Based on limited published data, efavirenz, emtricitabine, and tenofovir have been shown to be present in human breast milk.

It is not known if the components of efavirenz/emtricitabine/tenofovir disoproxil fumarate affect milk production or have effects on the breastfed child. Because of the potential for: (1) HIV transmission (in HIV-negative infants); (2) developing viral resistance (in HIV-positive infants); and (3) adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are receiving VIRADAY.

▶ Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy testing must be performed in adults and adolescents of childbearing potential before initiation of efavirenz/emtricitabine/tenofovir disoproxil fumarate because of potential risk of neural tube defects (see Use in Specific Populations).

Contraception

Adults and adolescents of childbearing potential must be advised on use of effective contraception during treatment with efavirenz/emtricitabine/tenofovir disoproxil fumarate and for 12 weeks after discontinuing efavirenz/emtricitabine/tenofovir disoproxil fumarate due to the long half-life of EFV, a component of efavirenz/emtricitabine/tenofovir disoproxil fumarate. Hormonal methods that contain progesterone may have decreased effectiveness. Always use barrier contraception in combination with other methods of contraception (see WARNING AND PRECAUTION- Drug Interactions).

▶ Pediatric Use

The effectiveness and safety of efavirenz/emtricitabine/tenofovir DF as a complete regimen for the treatment of HIV-1 infection was established in pediatric patients with body weight greater than or equal to 40 kg. Use of efavirenz/emtricitabine/tenofovir disoproxil fumarate in this age group is supported by adequate and well-controlled studies of efavirenz/emtricitabine/tenofovir disoproxil fumarate in adults with HIV-1 infection and data from pediatric studies of the individual components of (efavirenz/emtricitabine/tenofovir disoproxil fumarate).

Efavirenz/emtricitabine/tenofovir disoproxil fumarate should only be administered to pediatric patients with a body weight greater than or equal to 40 kg. Because VIRADAY is a fixed-dose combination tablet, the dose of efavirenz/emtricitabine/tenofovir disoproxil fumarate cannot be adjusted for patients of lower weight (see WARNINGS AND PRECAUTIONS, UNDESIRABLE EFFECTS).

▶ Geriatric Use

Clinical trials 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

Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate is not recommended for patients with moderate or severe hepatic impairment because there are insufficient data to determine an appropriate dose. Patients with mild hepatic impairment may be treated with efavirenz/emtricitabine/tenofovir disoproxil fumarate tablet at the approved dose. Because of the extensive cytochrome P450-mediated metabolism of efavirenz and limited clinical experience in patients with hepatic impairment, caution should be exercised in administering efavirenz/emtricitabine/tenofovir disoproxil fumarate to these patients (see DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS).

► Renal Impairment

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

Undesirable Effects

The following adverse reactions are discussed in other sections of the labeling:

Lactic acidosis/Severe hepatomegaly with steatosis (see WARNINGS AND PRECAUTIONS).

Severe acute exacerbations of hepatitis B in Patients Coinfected with HIV-1 and HBV (see WARNINGS AND PRECAUTIONS).

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).

Hepatotoxicity (see WARNINGS AND PRECAUTIONS).

Bone Loss and Mineralization defects (see WARNINGS AND PRECAUTIONS).

Immune reconstitution syndrome (see WARNINGS AND PRECAUTIONS).

Fat Redistribution (see WARNINGS AND PRECAUTIONS).

Embryo-Fetal Toxicity (see WARNINGS AND PRECAUTIONS).

Convulsions (see WARNINGS AND PRECAUTIONS).

► 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.

Clinical trials in Adults Subjects

Study 934

Study 934 was an open-label, active-controlled trial in which 511 antiretroviral-naïve subjects 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 greater than or equal to 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 trials of the individual components (Table 2).

Table 2: Selected treatment-emergent adverse reactions^a (Grades 2-4) reported in >5% in either 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 trial, 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/tenofovir disoproxil fumarate 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/tenofovir disoproxil fumarate 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 greater than or equal to 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.

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 trials (Table 3).

Table 3: Significant laboratory abnormalities reported in ≥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 ≥Grade 3 laboratory abnormality	30%	26%
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%
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^a From weeks 96 to 144 of the trial, 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.

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 trial due to hepatobiliary disorders (see WARNINGS AND PRECAUTIONS).

► Postmarketing Experience

The following adverse reactions 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, vertigo

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.

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, catatonia

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.

If you experience any side effects, talk to your doctor or pharmacist or write to drugsafety@cipa.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024.

By reporting side effects you can help provide more information on the safety of this product.

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

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

Tenofovir 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.

Storage And Handling Instructions

Store below 30°C. Protect from moisture

Packaging Information

VIRADAY.....Container of 30 tablets

Last Updated: August 2018

Last Reviewed: August 2018

VIRADAY Tablets

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