For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

Tenofovir Disoproxil Fumarate, Emtricitabine and Efavirenz Tablets

VIRADAY-V

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-V, IN COMBINATION WITH OTHER ANTIRETROVIRALS (SEE WARNINGS AND PRECAUTIONS).

VIRADAY-V IS NOT APPROVED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION AND THE SAFETY AND EFFICACY OF EFAVIRENZ/EMTRICITABINE/TENOFOVIR DISOPROXIL FUMARATE HAVE NOT BEEN ESTABLISHED IN PATIENTS COINFECTED 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-V. 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-V. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS AND PRECAUTIONS).

COMPOSITION :
Each film-coated tablet contains :
Tenofovir disoproxil fumarate ..... 300 mg
Emtricitabine..... 200 mg
Efavirenz USP..... 600 mg

DOSAGE FORM
Film coated tablet

DESCRIPTION
VIRADAY-V 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, β, and mitochondrial DNA polymerase γ.

Pharmacokinetics in Adults
Efavirenz/emtricitabine/tenofovir disoproxil fumarate: One **VIRADAY-V** 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 ± 3.7 µM (mean ± SD), C_{min} was 5.6 ± 3.2 µM, and AUC was 184 ± 73 µM•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 ± 0.7 µg/mL (mean ± SD) and the AUC over a 24-hour dosing interval was 10.0 ± 3.1 µg•hr/mL. The mean steady-state plasma trough concentration at 24 hours post-dose was 0.09 µg/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 µg/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 ± 89 ml/min (mean ± SD). Following a single oral dose, the plasma emtricitabine half-life is approximately 10 hours.

Tenofovir disoproxil fumarate
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 ± 0.4 hrs (mean ± SD) and C_{max} and AUC values were 296 ± 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 ± 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 has 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 disoproxil fumarate: 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 disoproxil fumarate: Efavirenz, emtricitabine, and tenofovir pharmacokinetics are similar in male and female subjects.

Pediatric Patients
VIRADAY-V should only be administered to pediatric patients 12 years of age and weighing greater than or equal to 40 kg (greater than or equal to 88 lb).

Efavirenz: In an open-label trial in NRTI-experienced pediatric subjects (mean age 8 years, range 3-16), the pharmacokinetics of efavirenz in pediatric subjects were similar to the pharmacokinetics in adults who received a 600 mg daily dose of efavirenz. In 48 pediatric subjects, receiving the equivalent of a 600 mg dose of efavirenz, mean (± SD) steady-state C_{max} was 14.2 ± 5.8 µM, steady-state C_{min} was 5.6 ± 4.1 µM, and AUC was 218 ± 104 µM•hr.

Emtricitabine: The pharmacokinetics of emtricitabine at steady state were determined in 27 HIV-1-infected pediatric subjects 13 to 17 years of age receiving a daily dose of 6 mg/kg up to a maximum dose of 240 mg oral solution or a 200 mg capsule; 26 of 27 subjects in this age group received the 200 mg emtricitabine capsule. Mean (± SD) C_{max} and AUC were 2.7 ± 0.9 µg/mL and 12.6 ± 5.4 µg•hr/mL, respectively. Exposures achieved in pediatric subjects 12 to less than 18 years of age were similar to those achieved in adults receiving a once daily dose of 200 mg.

Tenofovir Disoproxil Fumarate: Steady-state pharmacokinetics of tenofovir were evaluated in 8 HIV-1 infected pediatric subjects (12 to less than 18 years). Mean (± SD) C_{max} and AUC_{tau} are 0.38 ± 0.13 µg/mL and 3.39 ± 1.22 µg•hr/mL, respectively. Tenofovir exposure achieved in these pediatric subjects receiving oral daily doses of tenofovir disoproxil fumarate 300 mg was similar to exposures achieved in adults receiving once-daily doses of tenofovir disoproxil fumarate 300 mg.

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 disoproxil fumarate: 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 disoproxil fumarate: 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 pharmacokinetics in subjects with hepatic impairment compared with unimpaired subjects.

INDICATIONS
VIRADAY-V 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 and pediatric patients 12 years of age and older.

DOSAGE AND ADMINISTRATION
Adults and pediatric patients 12 years of age and older with body weight at least 40 kg (at least 88 lbs): The dose of **VIRADAY-V** is one tablet once daily taken orally on an empty stomach. Dosing at bedtime may improve the tolerability of nervous system symptoms.

Renal Impairment: Because **VIRADAY-V** 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 below 50 mL/min).

Rifampin Coadministration: When **VIRADAY-V** is administered with rifampin to patients weighing 50 kg or more, an additional 200 mg/day of efavirenz is recommended.

CONTRAINDICATIONS
Hypersensitivity
VIRADAY-V 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-V**.

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 (e.g., cardiac arrhythmias, prolonged sedation, or respiratory depression). Drugs that are contraindicated with efavirenz/emtricitabine/tenofovir disoproxil fumarate are listed in Table 1.

Table 1: Drugs That Are Contraindicated or Not Recommended for Use With Efavirenz/emtricitabine/tenofovir disoproxil fumarate

Drug Class: Drug Name	Clinical Comment
Antifungal: voriconazole	Efavirenz significantly decreases voriconazole plasma concentrations, and coadministration may decrease the therapeutic effectiveness of voriconazole. Also, voriconazole significantly increases efavirenz plasma concentrations, which may increase the risk of efavirenz-associated side effects. Because **VIRADAY-V** 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 (*Hypericum perforatum*)	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 or CYP2B6 (see **CONTRAINDICATIONS**).

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. *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 CYP3A activity (e.g., phenobarbital, rifampin, rifabutin) would be expected to increase the clearance of efavirenz, resulting in lowered plasma concentrations (see **DOSAGE AND ADMINISTRATION**).

Emtricitabine and Tenofovir disoproxil fumarate
Since emtricitabine and tenofovir are primarily eliminated by the kidneys, coadministration of **VIRADAY-V** with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of emtricitabine, tenofovir, and/or other renally eliminated 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.

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.

Darunavir with ritonavir and lopinavir/ritonavir have been shown to increase tenofovir concentrations. Tenofovir DF is a substrate of P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP) transporters. When tenofovir DF is co-administered with an inhibitor of these transporters, an increase in absorption may be observed. Patients receiving darunavir with ritonavir and **VIRADAY-V**, or lopinavir/ritonavir with **VIRADAY-V**, should be monitored for tenofovir-associated adverse reactions. **VIRADAY-V** should be discontinued in patients who develop tenofovir-associated adverse reactions (see Table 2).

Co-administration of atazanavir with **VIRADAY-V** is not recommended since coadministration 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 efavirenz/emtricitabine/tenofovir disoproxil fumarate (see Table 2).

Efavirenz, Emtricitabine and Tenofovir disoproxil fumarate
Other important drug interaction information for efavirenz/emtricitabine/tenofovir disoproxil fumarate is summarized in Table 1 and Table 2. The drug interactions described are based on trials conducted with efavirenz, emtricitabine or tenofovir DF as individual agents or are potential drug interactions; no drug interaction trials have been conducted using efavirenz/emtricitabine/tenofovir disoproxil fumarate. 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 Trials or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect	Clinical Comment
HIV antiviral agents		
Protease inhibitor: atazanavir	↓ atazanavir ↑ tenofovir	Co-administration of atazanavir with **VIRADAY-V** is not recommended. Co-administration of atazanavir with 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 concentrations. There are insufficient data to support dosing recommendations for atazanavir or atazanavir/ritonavir in combination with efavirenz/emtricitabine/tenofovir disoproxil fumarate.
Protease inhibitor: fosamprenavir calcium	↓ amprenavir	*Fosamprenavir (unboosted):* Appropriate doses of fosamprenavir and efavirenz/emtricitabine/tenofovir disoproxil fumarate with respect to safety and efficacy have not been established. *Fosamprenavir/ritonavir:* An additional 100 mg/day (300 mg total) of ritonavir is recommended when efavirenz/emtricitabine/tenofovir disoproxil fumarate is administered with fosamprenavir/ritonavir once daily. No change in the ritonavir dose is required when efavirenz/emtricitabine/tenofovir disoproxil fumarate is administered with fosamprenavir plus ritonavir twice daily.
Protease inhibitor: indinavir	↓ indinavir	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 ↑ tenofovir	Do not use once daily administration of lopinavir/ritonavir. Dose adjustment of lopinavir/ritonavir is recommended when coadministered with efavirenz. Refer to the full prescribing information for lopinavir/ritonavir for guidance on coadministration with efavirenz- or tenofovir-containing regimens, such as **VIRADAY-V**. Patients should be monitored for tenofovir-associated adverse reactions.
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 (e.g., dizziness, nausea, paresthesia) and laboratory abnormalities (elevated liver enzymes). Monitoring of liver enzymes is recommended when **VIRADAY-V** 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	Efavirenz decreases plasma concentrations of maraviroc. Refer to the full prescribing information for maraviroc for guidance on coadministration with **VIRADAY-V**.
NRTI: didanosine	↑ didanosine	Coadministration of **VIRADAY-V** and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse reactions including pancreatitis, lactic acidosis, and neuropathy. A dose reduction of didanosine is recommended when co-administered with tenofovir DF. For additional information on coadministration with tenofovir DF-containing products, please refer to the didanosine prescribing information.
NNRTI: Other NNRTIs	↑ or ↓ efavirenz and/or NNRTI	Combining two NNRTIs has not been shown to be beneficial. **VIRADAY-V** contains efavirenz and should not be coadministered with other NNRTIs.
Integrase strand transfer inhibitor: raltegravir	↓ raltegravir	Efavirenz reduces plasma concentrations of raltegravir. The clinical significance of this interaction has not been directly assessed.
Hepatitis C antiviral agents		
Protease inhibitor: boceprevir	↓ boceprevir	Plasma trough concentrations of boceprevir were decreased when boceprevir was coadministered with efavirenz, which may result in loss of therapeutic effect. The combination should be avoided.
Protease inhibitor: telaprevir	↓ telaprevir ↓ efavirenz	Concomitant administration of telaprevir and efavirenz resulted in reduced steady-state exposures to telaprevir and efavirenz.
Other agents		
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.
Antidepressants: bupropion	↓ buproprion	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 ↓ hydroxyitraconazole	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.
Anti-infective: clarithromycin	↓ clarithromycin ↑ 14-OH metabolite	Clinical significance unknown. In uninfected volunteers, 46% developed rash while receiving efavirenz and clarithromycin. No dose adjustment of efavirenz/emtricitabine/tenofovir disoproxil fumarate 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 disoproxil fumarate.
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 **VIRADAY-V** tablet is co-administered with rifampin to patients weighing 50 kg or more, an additional 200 mg/day of efavirenz is recommended.
Calcium channel blocker: diltiazem	↓ diltiazem ↓ desacetyl diltiazem ↓ N-monodesmethyl diltiazem	Diltiazem dose adjustments should be guided by clinical response (refer to the prescribing information for diltiazem). No dose adjustment of **VIRADAY-V** 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 complete prescribing information for the HMG-CoA reductase inhibitor for guidance on individualizing the dose.
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 (noreIgestromin and levonorgestrel) were markedly decreased. No effect of ethinyl estradiol/norgestimate on efavirenz plasma concentrations was observed.
Implant etonogestrel	↓ etonogestrel	A reliable method of barrier contraception must be used in addition to hormonal contraceptives. The interaction between etonogestrel and efavirenz has not been studied. Decreased exposure of etonogestrel may be expected. There have been postmarketing reports of contraceptive failure with etonogestrel in efavirenz-exposed patients.
Immunosuppressants: cyclosporine, tacrolimus, sirolimus,and others metabolized by CYP3A	↓ immuno-suppressant	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-V**.
Narcotic analgesic: methadone	↓ methadone	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.

[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-V**, 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-V** 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-V** is not approved for the treatment of chronic HBV infection, and the safety and efficacy of efavirenz/emtricitabine/tenofovir disoproxil fumarate have not been established in patients coinfected with HBV and HIV-1. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued emtricitabine and tenofovir DF, two of the components of **VIRADAY-V**. 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 coinfected 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-V**. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

VIRADAY-V should not be administered with adefovir dipivoxil (see **Drug Interactions**).

Coadministration with Related Products
Related drugs not for coadministration with **VIRADAY-V** include emtricitabine/rilpivirine/tenofovir DF, emtricitabine, elvitegravir/cobicistat/emtricitabine/tenofovir DF, emtricitabine/tenofovir DF, and tenofovir DF, which contain the same active components as **VIRADAY-V**. Efavirenz should not be coadministered with **VIRADAY-V** tablet unless needed for dose-adjustment (e.g. with rifampin) (see **DOSAGE AND ADMINISTRATION, Drug Interactions**). Due to similarities between emtricitabine and lamivudine, **VIRADAY-V** should not be coadministered with drugs containing lamivudine, including lamivudine/zidovudine, lamivudine or lamivudine-HBV, 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 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), 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 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 pscychiatric 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 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-to-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. 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 subjects 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-V** should be alerted to the potential for additive central nervous system effects when **VIRADAY-V** 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-V** is a combination product and the dose of the individual components cannot be altered, patients with estimated creatinine clearance below 50 mL/min should not receive **VIRADAY-V**.

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 estimated creatinine clearance be assessed in all patients prior to initiating therapy and as clinically appropriate during therapy with **VIRADAY-V**. In patients at risk of renal dysfunction, including patients who have previously experienced renal events while receiving adefovir dipivoxil, it is recommended that estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein be assessed prior to initiation of **VIRADAY-V**, and periodically during **VIRADAY-V** therapy.

VIRADAY-V should be avoided with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs)) (See **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.

Reproductive Risk Potential

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-V**. Barrier contraception must always be used in combination with other methods of contraception (e.g., oral or other hormonal contraceptives). Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of efavirenz/emtricitabine/tenofovir disoproxil fumarate is recommended. Women of childbearing potential should undergo pregnancy testing before initiation of **VIRADAY-V**. 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 trials of efavirenz/emtricitabine/tenofovir disoproxil fumarate in pregnant women. **VIRADAY-V** 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.

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 (e.g., 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). **VIRADAY-V** can be reinitiated in patients interrupting therapy because of rash. **VIRADAY-V** 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 (e.g., Stevens-Johnson syndrome), alternative therapy should be considered (see also **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 26 of 57 pediatric subjects (46%) treated with efavirenz (see **UNDESIRABLE EFFECTS**). One pediatric subject experienced Grade 3 rash (confluent rash with fever), and two subjects had Grade 4 rash (erythema multiforme). The median time to onset of rash in pediatric subjects was 8 days. Prophylaxis with appropriate antihistamines before initiating therapy with efavirenz/emtricitabine/tenofovir disoproxil fumarate in pediatric patients should be considered.

Hepatotoxicity

Monitoring of liver enzymes before and during treatment is recommended for patients with underlying hepatic disease, including hepatitis B or C infection; patients with marked transaminase elevations; and patients treated with other medications associated with liver toxicity. 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-V** needs to be weighed against the unknown risks of significant liver toxicity (See **UNDESIRABLE EFFECTS**).

Bone Effects of Tenofovir DF

Bone Mineral Density:

In clinical trials in HIV-1 infected adults, tenofovir DF 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. For more information, consult the tenofovir disoproxil fumarate prescribing information.

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.

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-V**. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections [such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia (PCP), or tuberculosis], which may necessitate further evaluation and treatment.

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. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Pregnancy

Pregnancy Category D

Efavirenz: As of July 2010, the Antiretroviral Pregnancy Registry has received prospective reports of 792 pregnancies exposed to efavirenz-containing regimens, nearly all of which were first-trimester exposures (718 pregnancies). Birth defects occurred in 17 of 604 live births (first-trimester exposure) and 2 of 69 live births (second/third-trimester exposure). 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; however, this case included severe oblique facial clefts and amniotic banding, a known association with anophthalmia. There have been six retrospective reports of findings consistent with neural tube defects, including meningomyelocele. All mothers were exposed to efavirenz-containing regimens in the first trimester. Although a causal relationship of these events to the use of efavirenz has not been established, similar defects have been observed in preclinical studies of efavirenz.

Animal Data

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, microophthalmia 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.

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 efavirenz is secreted in milk. Studies in human have shown that both tenofovir and efavirenz are excreted in human milk. Because the risks of low exposure to emtricitabine and tenofovir to infants are unknown, and because of the potential for HIV-1 transmission, **mothers should be instructed not to breastfeed if they are receiving VIRADAY-V**.

Emtricitabine

Samples of breast milk obtained from five HIV-1 infected mothers show that emtricitabine is secreted in human milk. Breastfeeding infants whose mothers are being treated with emtricitabine may be at risk for developing viral resistance to emtricitabine. Other emtricitabine-associated risks in infants breastfed by mothers being treated with emtricitabine are unknown.

Tenofovir Disoproxil Fumarate

Samples of breast milk obtained from five HIV-1 infected mothers show that tenofovir is secreted in human milk. Tenofovir-associated risks, including the risk of viral resistance to tenofovir, in infants breastfed by mothers being treated with tenofovir disoproxil fumarate are unknown.

Pediatric Use

VIRADAY-V should only be administered to pediatric patients 12 years of age and older with a body weight greater than or equal to 40 kg (greater than or equal to 88 lbs). Because **VIRADAY-V** is a fixed-dose combination tablet, the dose adjustments recommended for pediatric patients younger than 12 years of age for each individual component cannot be made with **VIRADAY-V**. (See **PHARMACOLOGY AND 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

VIRADAY-V 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 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 **VIRADAY-V** to these patients.

Renal Impairment

Because **VIRADAY-V** 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 below 50 mL/min).

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**).
- 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 Effects of Tenofovir DF (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.

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 3).

Table 3: 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 + tenofovir DF with efavirenz.

[c] Rash event includes rash, exfoliative rash, rash generalized, rash macular, rash maculopapular, 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 disoproxil fumarate 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-to-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.

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.

Clinical Trials in Pediatric Subjects

Efavirenz: In a pediatric clinical trial in 57 NRTI-experienced subjects aged 3 to 16 years, the type and frequency of adverse experiences was generally similar to that of adult subjects with the exception of a higher incidence of rash, which was reported in 46% (26/57) of pediatric subjects compared to 26% of adults, and a higher frequency of Grade 3 or 4 rash reported in 5% (3/57) of pediatric subjects compared to 0.9% of adults (see **WARNINGS AND PRECAUTIONS**). For additional information, please consult the Efavirenz prescribing information.

Emtricitabine: In addition to the adverse reactions reported in adults, anemia and hyperpigmentation were observed in 7% and 32%, respectively, of pediatric subjects (3 months to less than 18 years of age) who received treatment with emtricitabine in the larger of two open-label, uncontrolled pediatric trials (N=116). For additional information, please consult the Emtricitabine prescribing information.

Tenofovir Disoproxil Fumarate: In a pediatric clinical trial conducted in subjects 12 to less than 18 years of age, the adverse reactions observed in pediatric subjects who received treatment with tenofovir DF were consistent with those observed in clinical trials of tenofovir DF in adults (see **WARNINGS AND PRECAUTIONS**).

Laboratory Abnormalities

Efavirenz, Emtricitabine and Tenofovir Disoproxil Fumarate: Laboratory abnormalities observed in Study 934 were generally consistent with those seen in previous trials (Table 4).

Table 4: 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/mm³)	3%	5%
Fasting Triglycerides (>750 mg/dL)	4%	2%

[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.

In addition to the laboratory abnormalities described for Study 934 (Table 4), Grade 3/4 laboratory abnormalities of increased bilirubin (greater than 2.5 x upper limit of normal (ULN)), increased pancreatic amylase (greater than 2.0 x ULN), increased or decreased serum glucose (less than 40 or greater than 250 mg/dL), and increased serum lipase (greater than 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 coinfected 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 coinfected subject discontinued from the trial due to hepatobiliary disorders (see **WARNINGS AND PRECAUTIONS**).

Postmarketing Experience

The following adverse reactions have been identified during postapproval 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. 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

Pancreatitis, increased amylase, abdominal pain

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 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 trial single doses of emtricitabine 1200 mg were administered to 11 subjects. No severe adverse reactions were reported.

Hemodialysis treatment removes approximately 30% of the emtrictabine 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 disoproxil fumarate

Limited clinical experience at doses higher than the therapeutic dose of tenofovir DF 300 mg is available. In one trial, 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.

INCOMPATIBILITY : Not applicable

SHELF-LIFE : 36 Months

STORAGE : Do not store above 30°C. Protect from light.

PACKAGING INFORMATION

VIRADAY-V.....Container of 30 tablets

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