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

VIRADAY TABLETS

(Tenofovir Disoproxil Fumarate 300 mg + Emtricitabine 200 mg + Efavirenz 600 mg Tablets)

WARNING

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

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

VIRADAY IS NOT APPROVED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION AND THE SAFETY AND EFFICACY OF VIRADAY HAVE NOT BEEN ESTABLISHED IN PATIENTS CO-INFECTED WITH HVB AND HIV-1. SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO HAVE DISCONTINUED EMTRICITABINE, OR TENOFOVIR DISOPROXIL FUMARATE, WHICH ARE COMPONENTS OF VIRADAY. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO ARE COINFECTED WITH HIV-1 AND HBV AND DISCONTINUE VIRADAY. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED.

COMPOSITION

Each film-coated tablet contains

Tenofovir disoproxil fumarate ..... 300 mg
Equivalent to Tenofovir disoproxil ..... 245 mg
Emtricitabine .....200 mg
Efavirenz ..... 600 mg
Colours: Red Oxide of iron, Yellow Oxide of Iron, Titanium Dioxide

DOSAGE FORM

Oral, fixed-dose tablet

DESCRIPTION

Pink coloured, capsule shaped, biconvex film coated tablets with “V” debossed on one side and plain on other side.

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, Є and mitochondrial DNA polymerase, γ.

Tenofovir Disoproxil Fumarate (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.

Cardiac Electrophysiology

The effect of VIRADAY 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 health subjects enriched for CYP2B6 polymorphisms. The mean Cmax of efavirenz in subjects with CYP2B6 *6/*6 genotype following the administration of 600mg daily dose for 14 days was 2.25-fold the mean Cmax 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 8.7ms and 11.3ms in subjects with CYP2B6*6/*6 genotype following the administration of 600mg daily dose for 14 days (see *Section Warnings and Precautions and Section Interactions with Other Medicaments).*

Pharmocokinetics in Adults

Forty-five healthy volunteers completed a single-dose, fasted-state pharmacokinetic and bioequivalence study of the co-formulation versus the three individual agents. The geometric mean ratios of the coformulation to the single agents combination for Cmax, AUC0-τ and AUC0-∞ ranged from 0.89 to 1.0, with 90% CI ranging 84 – 108%, indicating that the two comparators were bioequivalent for all three components, based on these pharmacokinetic parameters (bioequivalence range is 80 – 125%).[1]

The maximum concentration of efavirenz occurs at 2 – 4 h postdose, and are 2.5 – 4.0 mg/l, and minimum concentrations are 1.0 – 1.7 mg/l. Oral clearance is 10 – 16 l/h, with apparent volume of distribution of

350 – 550 l. Efavirenz is 99.5 – 99.75% protein bound, mainly to albumin. AUC at steady-state ranges from 35 – 60 mg/h/l. CYP2B6 and CYP3A4 are the major isozymes that metabolize efavirenz, and efavirenz induces CYP450 enzymes, thereby inducing its own metabolism. A G516T *CYP2B6* gene substitution has been associated with clinically significant differences in the clearance rates of efavirenz. Individuals that are carriers of wild-type GG genotype have the shortest median plasma half-lifes of 23 h, but those with TT genotype have longer median half-lifes of 48 h.[1]

The maximum emtricitabine plasma concentrations of 1.5 – 2.0 mg/l occurs at 1 – 2 h post dose, with minimum concentrations of 0.04 – 0.09 mg/l. Bioavailability is high at 93%, with < 4% protein bound. Emtricitabine is primarily eliminated via the kidneys, with an oral clearance of 20 l/h. The AUC0-24 is 7 – 10 mg/h/l. The plasma t½ is 7 – 10 h, with an intracellular t½ of the triphosphate active metabolite of 39 h.[1]

The tenofovir plasma Cmax is 0.3 – 0.4 mg/l and achieved at 2 – 3 h post dose. Minimum concentrations are 0.06 mg/l, with an AUC0-24 of 2 – 3 mg/h/l. Oral clearance is 35 – 40 l/h. Protein binding is low at < 0.7%, with 70 – 80% of systemically available tenofovir eliminated unchanged in urine. The plasma t½ of tenofovir is 12 – 17 h. The intracellular t½ of the tenofovir diphosphate is approximately > 60 h.[1]

Special Populations

<u>*Race*</u>

Efavirenz: The pharmacokinetics of efavirenz appears to be similar among the racial groups studied.

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

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

<u>*Gender*</u>

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

<u>*Pediatric and Geriatric Patients*</u>

VIRADAY is not recommended for pediatric administration. Pharmacokinetics of efavirenz, emtricitabine and tenofovir DF have not been fully evaluated in the elderly (>65 years of age).

<u>*Patients with Impaired Renal Function*</u>

In patients with creatinine clearance < 50 ml/min, emtricitabine and tenofovir exposure are increased, and a dose reduction is recommended by the manufacturer. In contrast, the elimination profile of efavirenz in

these patients remains unchanged. For this reason, patients with creatinine clearance values < 50 ml/min should not receive VIRADAY.

Patients with Hepatic Impairment

Efavirenz: No significant effect on efavirenz pharmacokinetics was seen 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.

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.

PRECLINICAL SAFETY DATA

Carcinogenesis, Mutagenesis, Impairment of Fertility

Efavirenz: Long-term carcinogenicity studies in mice and rats were carried out with efavirenz. Mice were dosed with 0, 25, 75, 150, or 300 mg/kg/day for 2 years. Incidences of hepatocellular adenomas and carcinomas and pulmonary alveolar/bronchiolar adenomas were increased above background in females. No increases in tumor incidence above background were seen in males. In studies in which rats were administered efavirenz at doses of 0, 25, 50, or 100 mg/kg/day for 2 years, no increases in tumor incidence above background were observed. The systemic exposure (based on AUCs) in mice was approximately 1.7-fold that in humans receiving the 600-mg/day dose. The exposure in rats was lower than that in humans. The mechanism of the carcinogenic potential is unknown. However, in genetic toxicology assays, efavirenz showed no evidence of mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* studies. These included bacterial mutation assays in *S. typhimurium* and *E.coli*, mammalian mutation assays in Chinese hamster ovary cells, chromosome aberration assays in human peripheral blood lymphocytes or Chinese hamster ovary cells, and an *in vivo* mouse bone marrow micronucleus assay. Given the lack of genotoxic activity of efavirenz, the relevance to humans of neoplasms in efavirenz-treated mice is not known.

Efavirenz did not impair mating or fertility of male or female rats, and did not affect sperm of treated male rats. The reproductive performance of offspring born to female rats given efavirenz was not

affected. As a result of the rapid clearance of efavirenz in rats, systemic drug exposures achieved in these studies were equivalent to or below those achieved in humans given therapeutic doses of efavirenz.

Emtricitabine: In long-term carcinogenicity studies of emtricitabine, no drug-related increases in tumor incidence were found in mice at doses up to 750 mg/kg/day (26 times the human systemic exposure at the therapeutic dose of 200 mg/day) or in rats at doses up to 600 mg/day (31 times the human systemic exposure at the therapeutic dose).
Emtricitabine was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or mouse micronucleus assays.

Emtricitabine did not affect fertility in male rats at approximately 140-fold or in male and female mice at approximately 60-fold higher exposures (AUC) than in humans given the recommended 200 mg daily dose. Fertility was normal in the offspring of mice exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately 60-fold higher than human exposures at the recommended 200 mg daily dose.

Tenofovir Disoproxil Fumarate: Long-term oral carcinogenicity studies of tenofovir DF in mice and rats were carried out at exposures up to approximately 16 times (mice) and 5 times (rats) those observed in humans at the therapeutic dose for HIV-1 infection. At the high dose in female mice, liver adenomas were increased at exposures 16 times that in humans. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose.

Tenofovir DF was mutagenic in the *in vitro* mouse lymphoma assay and negative in an *in vitro* bacterial mutagenicity test (Ames test). In an *in vivo* mouse micronucleus assay, tenofovir DF was negative when administered to male mice.

There were no effects on fertility, mating performance or early embryonic development when tenofovir DF was administered to male rats at a dose equivalent to 10 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 15 days prior to mating through day seven of gestation. There was, however, an alteration of the estrous cycle in female rats.[2]

Animal Toxicology and/or Pharmacology
Efavirenz: Nonsustained convulsions were observed in 6 of 20 monkeys receiving efavirenz at doses yielding plasma AUC values 4- to 13-fold greater than those in humans given the recommended dose.

Tenofovir Disoproxil Fumarate: Tenofovir and tenofovir DF administered in toxicology studies to rats, dogs and monkeys at exposures (based on AUCs) greater than or equal to 6-fold those observed in humans caused bone toxicity. In monkeys the bone toxicity was diagnosed as osteomalacia. Osteomalacia observed in monkeys appeared to be reversible upon dose reduction or discontinuation of tenofovir. In

rats and dogs, the bone toxicity manifested as reduced bone mineral density. The mechanism(s) underlying bone toxicity is unknown.

Evidence of renal toxicity was noted in 4 animal species administered tenofovir and tenofovir DF. Increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia and/or calciuria and decreases in serum phosphate were observed to varying degrees in these animals. These toxicities were noted at exposures (based on AUCs) 2 to 20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia, to the bone toxicity is not known.[2]

INDICATIONS

VIRADAY is indicated for the treatment of HIV-1 infection in adults.

DOSAGE AND ADMINISTRATION

Adults

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

Pediatrics

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

Renal Impairment

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

Rifampicin Coadministration

When VIRADAY is administered with rifampicin to patients weighing 50 kg or more, an additional 200 mg/day of efavirenz is recommended.

CONTRAINDICATIONS

VIRADAY is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the product.[3]

Table 1: Drugs That Are Contraindicated or Not Recommended for Use with VIRADAY.

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 is a fixed-dose combination product, the dose of efavirenz cannot be altered.
Antimigraine: Ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine)	Potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
Benzodiazepines: midazolam, triazolam	Potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.
Calcium channel blocker: bepridil	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
GI motility agent: cisapride	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Neuroleptic: pimozide	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
St. John's wort (*Hypericum perforatum*)	May lead to loss of virologic response and possible resistance to efavirenz or to the class of nonnucleoside reverse transcriptase inhibitors (NNRTIs).

Pediatric Use

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

Geriatric Use

Clinical trials of efavirenz, emtricitabine, or tenofovir disoproxil fumarate 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 is not recommended for patients with moderate or severe hepatic impairment because there are insufficient data.

Renal Impairment

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

WARNINGS AND PRECAUTIONS

General

VIRADAY should be taken cautiously in patients with bone, kidney or liver problems in anamnesis as well as in patients with psychiatric disorders and addictions.[3]

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs including tenofovir DF, a component of VIRADAY, in combination with other antiretrovirals. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with VIRADAY should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).[2]

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. 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. If appropriate, initiation of anti-hepatitis B therapy may be warranted. VIRADAY should not be administered with adefovir dipivoxil.[2]

Coadministration with Related Products

Related drugs not for coadministration with VIRADAY include emtricitabine/rilpivirine/tenofovir DF, emtricitabine, tenofovir DF, and emtricitabine/tenofovir DF, which contain the same active components as VIRADAY. Efavirenz should not be coadministered with VIRADAY unless needed for dose-adjustment (e.g. with rifampicin). Due to similarities between emtricitabine and lamivudine, VIRADAY should not be coadministered with drugs containing lamivudine, including lamivudine/zidovudine, or lamivudine, abacavir sulfate/lamivudine, or abacavir sulfate/lamivudine/zidovudine.[2]

Psychiatric Symptoms

Serious psychiatric adverse experiences have been reported in patients treated with efavirenz. Specific serious psychiatric events observed were severe depression, suicidal ideation, nonfatal suicide attempts, aggressive behavior, paranoid reactions, and manic reactions. 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.[2]

New Onset or Worsening Renal Impairment

Emtricitabine and tenofovir are principally eliminated by the kidney; however, efavirenz is not. Since VIRADAY is a combination product and the dose of the individual components cannot be altered, patients with creatinine clearance below 50 mL/min should not receive VIRADAY. Renal impairment, including cases of acute renal failure and Fanconi syndrome has been reported with the use of tenofovir disoproxil fumarate. Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment, including patients who have previously experienced renal events while receiving adefovir dipivoxil. VIRADAY should be avoided with concurrent or recent use of a nephrotoxic agent.[2]

Rash

Rash associated with blistering, moist desquamation, or ulceration are seen when treated with efavirenz. VIRADAY can be reinitiated in patients interrupting therapy because of rash. VIRADAY should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement, or fever. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash.[2]

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. Liver enzyme monitoring should also be considered for patients without pre-existing hepatic dysfunction or other risk factors.[2]

Decreases in Bone Mineral Density

Assessment of bone mineral density (BMD) should be considered for 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.[2]

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.[2]

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including the components of VIRADAY. During the initial phase of combination antiretroviral treatment, patients whose immune system responds to such treatment may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment. 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.[2]

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.[2]

Cardiac Electrophysiology

QTc prolongation has been observed with the use of efavirenz (see *Section Pharmacodynamics and Section Interactions with Other Medicaments*). Consider alternatives to VIRADAY 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.

Nervous System Symptoms

Late-onset neurotoxicity, including ataxia and encephalopathy (impaired consciousness, confusion, psychomotor slowing, psychosis, delirium), may occur months to years after beginning efavirenz therapy. Some events of late-onset neurotoxicity have occurred in patients with CYP2B6 generic polymorphisms, which are associated with increased efavirenz levels despite standard dosing of VIRADAY. Patients presenting with signs and symptoms of serious neurologic adverse experiences should be evaluated promptly to assess the possibility that these events may be related to efavirenz use, and whether discontinuation of VIRADAY is warranted.

INTERACTIONS WITH OTHER MEDICAMENTS

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. Coadministration of efavirenz with drugs primarily metabolized by these isozymes may result in altered plasma concentrations of the co-administered drug. Therefore, appropriate dose adjustments may be

necessary for these drugs. Drugs that induce CYP3A activity (e.g., phenobarbital, rifampicin, rifabutin) would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations.[2]

Since emtricitabine and tenofovir are primarily eliminated by the kidneys, coadministration of VIRADAY with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of emtricitabine, tenofovir, and/or other renally eliminated drugs. Some examples include, but are not limited to, acyclovir, adefovir dipivoxil, cidofovir, ganciclovir, valacyclovir, and valganciclovir. Coadministration of tenofovir DF and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse reactions. Didanosine should be discontinued in patients who develop didanosine-associated adverse reactions. Suppression of $CD4^+$ cell counts has been observed in patients receiving tenofovir DF with didanosine 400 mg daily.[2]

Lopinavir/ritonavir has been shown to increase tenofovir concentrations. Patients receiving lopinavir/ritonavir with VIRADAY should be monitored for tenofovir-associated adverse reactions. VIRADAY should be discontinued in patients who develop tenofovir-associated adverse reactions. Coadministration of atazanavir with VIRADAY 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.[2]

VIRADAY should not be administered concurrently with midazolam, triazolam, pimozide, bepridil, terfenadine, astemizole, cisapride, or ergot alkaloids because competition for CYP3A4 liver enzymes by Efavirenz what could result in inhibition of metabolism of these drugs and could be responsible for serious adverse events, including cardiac arrhythmias, prolonged or increased sedation and respiratory depression. VIRADAY also should not be co-administered with voriconazole, because Efavirenz significantly decreases its plasma concentrations. Drug should not be used during pregnancy unless clearly necessary, moreover pregnancy should be avoided in women receiving VIRADAY. Effective contraception should always be used (moreover because of the long half-life of Efavirenz, it is recommended for 12 weeks after discontinuation of treatment).[3]

Table 2: Established and other potentially significant drug interactions

Concomitant Drug Class: Drug Name	Effect	Clinical Comment
Antiretroviral Agents		
Protease inhibitor: Atazanavir	↓ atazanavir concentration ↑ tenofovir concentration	Co-administration of atazanavir with **VIRADAY** is not recommended. Co-administration of atazanavir with either efavirenz or tenofovir disoproxil fumarate 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 5 concentrations. There are insufficient data to support dosing recommendations for atazanavir or atazanavir/ritonavir in combination with **VIRADAY**.
Protease inhibitor: Fosamprenavir calcium	↓ amprenavir concentration	*Fosamprenavir (unboosted):* Appropriate doses of fosamprenavir and VIRADAY 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 VIRADAY is administered with fosamprenavir/ritonavir once daily. No change in the ritonavir dose is required when VIRADAY is administered with fosamprenavir plus ritonavir twice daily.
Protease inhibitor: Indinavir	↓ indinavir concentration	The optimal dose of indinavir, when given in combination with efavirenz, is not known. Increasing the indinavir dose to 1000 mg every 8 hours does not compensate for the increased indinavir metabolism due to efavirenz.
Protease inhibitor: Lopinavir/ritonavir	↓ lopinavir concentration ↑ tenofovir concentration	A dose increase of lopinavir/ritonavir to 600/150 mg (3 tablets) may be considered when used in combination with efavirenz in treatment-experienced patients where decreased susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). **Patients should be monitored for tenofovir-associated adverse reactions.** VIRADAY **should be discontinued in patients who develop tenofovir DF-associated adverse reactions**.

Protease inhibitor: Ritonavir	↑ ritonavir concentration ↑ efavirenz concentration	When ritonavir 500 mg every 12 hours was coadministered with efavirenz 600 mg once daily, combination was associated with a higher frequency of adverse clinical experiences (eg, dizziness, nausea, paresthesia) and laboratory abnormalities (elevated liver enzymes). Monitoring of liver enzymes is recommended when VIRADAY is used in combination with ritonavir.
Protease inhibitor: Saquinavir	↓ saquinavir concentration	Should not be used as sole protease inhibitor in combination with VIRADAY.
CCR5 co-receptor antagonist: Maraviroc	↓ maraviroc concentration	Efavirenz decreases plasma concentrations of maraviroc. Refer to the full prescribing information for maraviroc for guidance on coadministration with VIRADAY.
NRTI: Didanosine	↑ didanosine concentration	Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis and neuropathy. **In adults weighing >60 kg, the didanosine dose should be reduced to 250 mg if coadministered with** VIRADAY**. Data are not available to recommend a dose adjustment of didanosine for patients weighing <60 kg. Coadministration of** VIRADAY **and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse reactions. For additional information, please consult the didanosine prescribing information.**
Other Agents		
Anticoagulant: Warfarin	↑or ↓ warfarin concentration	Plasma concentrations and effects potentially increased or decreased by efavirenz.

Anticonvulsants: Carbamazepine	↓ carbamazepine concentration ↓ efavirenz concentration	There are insufficient data to make a dose recommendation for VIRADAY. Alternative anticonvulsant treatment should be used.
Phenytoin	↓ anticonvulsant concentration	Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.
Phenobarbital	↓efavirenz concentration	
Antidepressants: Bupropion	↓ bupropion concentration	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 concentration	Increases in sertraline dose should be guided by clinical response.
Antifungals: Itraconazole	↓ itraconazole concentration ↓ hydroxyitraconazole concentration	Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered.
Ketoconazole	↓ ketoconazole concentration	Drug interaction trials with VIRADAY and ketoconazole have not been conducted. Efavirenz has the potential to decrease plasma concentrations of ketoconazole.
Posaconazole	↓ posaconazole concentration	Avoid concomitant use unless the benefit outweighs the risks.
Anti-infective: Clarithromycin	↓ clarithromycin concentration ↑ 14-OH metabolite concentration	Clinical significance unknown. In uninfected volunteers, 46% developed rash while receiving efavirenz and clarithromycin. No dose adjustment of VIRADAY is recommended when given

		with clarithromycin. Alternatives to clarithromycin, such as azithromycin, should be considered. Other macrolide antibiotics, such as erythromycin, have not been studied in combination with VIRADAY.
Antimycobacterial: Rifabutin	↓ rifabutin concentration	Increase daily dose of rifabutin by 50%. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week
Antimycobacterial: Rifampicin	↓ efavirenz concentration	If VIRADAY is coadministered with rifampicin to patients weighing 50 kg or more, an additional 200 mg/day of efavirenz is recommended.
Calcium channel blockers: Diltiazem	↓ diltiazem concentration ↓ desacetyl diltiazem concentration ↓ N-monodesmethyl diltiazem concentration	Diltiazem dose adjustments should be guided by clinical response (refer to the prescribing information for diltiazem). No dose adjustment of VIRADAY is necessary when administered with diltiazem.
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 prescribing information for the calcium channel blocker).
HMG-CoA reductase inhibitors: Atorvastatin Pravastatin	↓ atorvastatin concentration ↓ pravastatin	Plasma concentrations of atorvastatin, pravastatin and simvastatin decreased. Consult the complete prescribing information for the HMG-CoA reductase inhibitor for guidance on individualizing

Simvastatin	concentration ↓ simvastatin concentration	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 (norelgestromin and levonorgestrel) were markedly decreased. No effect of ethinyl estradiol/norgestimate on efavirenz plasma concentrations was observed.
Implant Etonogestrel	↓ etonogestrel	A reliable method of barrier contraception must be used in addition to hormonal contraceptives. The interaction between etonogestrel and efavirenz has not been studied. Decreased exposure of etonogestrel may be expected. There have been postmarketing reports of contraceptive failure with etonogestrel in efavirenz-exposed patients.
Immunosuppressants: Cyclosporine, tacrolimus, sirolimus,and others metabolized by CYP3A	↓ immunosuppressant	Decreased exposure of the immunosuppressant may be expected due to CYP3A induction by efavirenz. These immunosuppressants are not anticipated to affect exposure of efavirenz. Dose adjustments of the immunosuppressant may be required. Close monitoring of immunosuppressant concentrations for at least 2 weeks (until stable concentrations are reached) is recommended when starting or stopping treatment with VIRADAY.
Narcotic analgesic: Methadone	↓ methadone concentration	Co-administration of efavirenz in HIV-1-infected individuals with a history of injection drug use resulted in decreased

		plasma levels of methadone and signs of opiate withdrawal. Methadone dose was increased by a mean of 22% to alleviate withdrawal symptoms. Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.
QT Prolonging Drugs	NA	There is limited information available on the potential for a pharmacodynamic interaction between VIRADAY and drugs that prolong the QTc interval. QTc prolongation has been observed with the use of efavirenz (see *Section Pharmacodynamics and Section Warnings and Precautions*). Consider alternatives to VIRADAY when co-administered with a drug with a known risk of Torsade de Pointes.

[a] This table is not all-inclusive.

PREGNANCY AND LACTATION

Pregnancy Category D:

Efavirenz may cause fetal harm when administered during the first trimester to a pregnant woman. Pregnancy should be avoided in women receiving VIRADAY. Barrier contraception 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 VIRADAY is recommended. Women of childbearing potential should undergo pregnancy testing before initiation of VIRADAY. If this drug is used during the first trimester of pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus. VIRADAY should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus, such as in pregnant women without other therapeutic options.[2]

Malformations have been observed in 3 of 20 fetuses/infants from efavirenz-treated cynomolgus monkeys (versus 0 of 20 concomitant controls) in a developmental toxicity study. The pregnant monkeys were dosed throughout pregnancy (post-coital days 20-150) with efavirenz 60 mg/kg daily, a dose which resulted in plasma drug concentrations similar to those in humans given 600 mg/day of efavirenz. Anencephaly and unilateral anophthalmia were observed in one fetus, microophthalmia was observed in

another fetus, and cleft palate was observed in a third fetus. Efavirenz crosses the placenta in cynomolgus monkeys and produces fetal blood concentrations similar to maternal blood concentrations. Efavirenz has been shown to cross the placenta in rats and rabbits and produces fetal blood concentrations of efavirenz similar to maternal concentrations. An increase in fetal resorptions was observed in rats at efavirenz doses that produced peak plasma concentrations and AUC values in female rats equivalent to or lower than those achieved in humans given 600 mg once daily of efavirenz. Efavirenz produced no reproductive toxicities when given to pregnant rabbits at doses that produced peak plasma concentrations similar to and AUC values approximately half of those achieved in humans given 600 mg once daily of efavirenz.

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. It is not known whether efavirenz, tenofovir or emtricitabine are excreted in human milk. Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving VIRADAY**.

UNDESIRABLE EFFECTS

In a study to assess effectiveness and safety of a generic fixed-dose combination of tenofovir (TDF)/emtricitabine (FTC)/efavirenz (EFV) among HIV-1-infected patients in Western India the major toxicity associated with TDF/FTC/EFV was EFV induced CNS neuropsychiatric manifestations. Ninety-six percent of patients were virologically suppressed at 6 months. Frequency of TDF-associated grade 34 renal toxicity was 2.8%; however, 3 of these patients had comorbid conditions associated with renal dysfunction.[4]

The frequency of adverse events associated with other drugs in the regimen (FTC, EFV) was similar to that described when these drugs were used in non-TDF-based regimens.[4]

The most significant adverse reactions linked with Efavirenz use are CNS and psychiatric symptoms as headache, disturbance in attention, abnormal dreams, somnolence, insomnia, depression (severe in 1.6%), and anxiety. However, dosing at bedtime may improve the tolerability of nervous system symptoms. Moreover, these psychiatric and CNS side effects related to efavirenz usually begin during the first one or two days of therapy and generally resolve after the first two to four weeks. The other possible side effects associated with Tenofovir disoproxil fumarate are kidney function decline or failure and bone abnormalities. Renal function (creatinine clearance and serum phosphate) should be monitored every 4 weeks during the first year and then every 3 months. VIRADAY is not recommended for patients with moderate or severe renal impairment (creatinine clearance <50 ml/min).[3]

Post-marketing experiences: Encephalopathy

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 disoproxil fumarate (refer to detailed information below), but is unlikely to significantly remove efavirenz from the blood.

Efavirenz: Increased nervous system symptoms and involuntary muscle contractions have been reported.

Emtricitabine: Limited clinical experience is available at doses higher than the therapeutic dose of emtricitabine. No severe adverse reactions were reported with single doses of emtricitabine 1200 mg.

It is not known whether emtricitabine can be removed by peritoneal dialysis.

Tenofovir DF: Limited clinical experience at doses higher than the therapeutic dose of tenofovir disoproxil fumarate 300 mg is available. 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 disoproxil fumarate, a 4-hour hemodialysis session removed approximately 10% of the administered tenofovir disoproxil fumarate dose.

STORAGE AND HANDLING INSTRUCTIONS

Store below 30^0C.

SHELF-LIFE

36 months

PACK SIZE

Carton containing plastic container of 30 tablets each.

PRODUCT REGISTRATION HOLDER

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