CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-752

APPROVED LABELING

TRUVADA®

(emtricitabine and tenofovir disoproxil fumarate)

Tablets

℞ Only

WARNING

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

TRUVADA® IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION AND THE SAFETY AND EFFICACY OF TRUVADA HAVE NOT BEEN ESTABLISHED IN PATIENTS COINFECTED WITH HBV AND HIV. SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO HAVE DISCONTINUED EMTRIVA® or VIREAD®. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE TRUVADA AND ARE COINFECTED WITH HIV AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS).

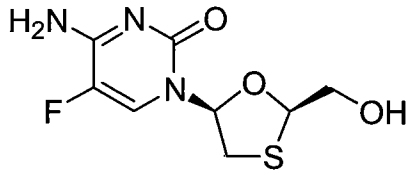
DESCRIPTION

TRUVADA Tablets are fixed dose combination tablets containing emtricitabine and tenofovir disoproxil fumarate. EMTRIVA is the brand name for emtricitabine, a synthetic nucleoside analog of cytidine. Tenofovir disoproxil fumarate (VIREAD, also known as tenofovir DF) is converted in vivo to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate. Both emtricitabine and tenofovir exhibit inhibitory activity against HIV-1 reverse transcriptase.

TRUVADA Tablets are for oral administration. Each film-coated tablet contains 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate, (which is equivalent to 245 mg of tenofovir disoproxil), as active ingredients. The tablets also include the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and pregelatinized starch (gluten free). The tablets are coated with Opadry II Blue Y-30-10701, which contains FD&C Blue #2 aluminum lake, hypromellose, lactose monohydrate, titanium dioxide, and triacetin.

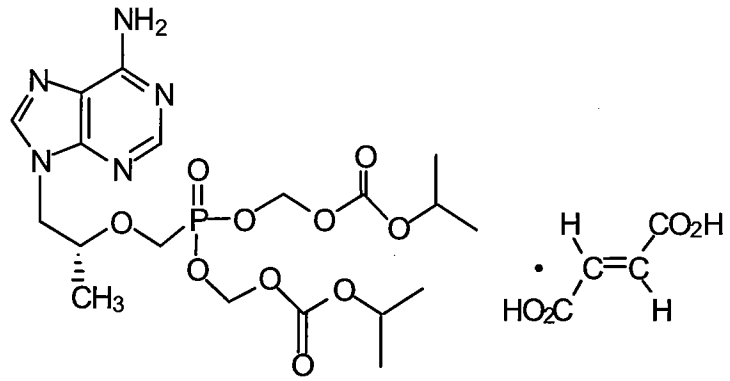
Emtricitabine: The chemical name of emtricitabine is 5-fluoro-1-(2*R*,5*S*)-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. Emtricitabine is the (-) enantiomer of a thio analog of cytidine, which differs from other cytidine analogs in that it has a fluorine in the 5-position.

It has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.24. It has the following structural formula:



Emtricitabine is a white to off-white crystalline powder with a solubility of approximately 112 mg/mL in water at 25 °C. The partition coefficient (log p) for emtricitabine is -0.43 and the pKa is 2.65.

Tenofovir disoproxil fumarate: Tenofovir disoproxil fumarate is a fumaric acid salt of the bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. The chemical name of tenofovir disoproxil fumarate is 9-[(*R*)-2 [[bis[[(isopropoxycarbonyl)oxy]-methoxy]phosphinyl]methoxy]propyl]adenine fumarate (1:1). It has a molecular formula of $C_{19}H_{30}N_5O_{10}P \bullet C_4H_4O_4$ and a molecular weight of 635.52. It has the following structural formula:



Tenofovir disoproxil fumarate is a white to off-white crystalline powder with a solubility of 13.4 mg/mL in water at 25 °C. The partition coefficient (log p) for tenofovir disoproxil is 1.25 and the pKa is 3.75. All dosages are expressed in terms of tenofovir disoproxil fumarate except where otherwise noted.

MICROBIOLOGY

Mechanism of Action

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 reverse transcriptase (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 disoproxil fumarate: Tenofovir disoproxil fumarate is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir disoproxil fumarate 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.

Antiviral Activity

Emtricitabine and tenofovir disoproxil fumarate: In combination studies evaluating the in vitro antiviral activity of emtricitabine and tenofovir together, synergistic antiviral effects were observed.

Emtricitabine: The in vitro antiviral activity of emtricitabine against laboratory and clinical isolates of HIV was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. The IC_{50} values for emtricitabine were in the range of 0.0013–0.64 µM (0.0003–0.158 µg/mL). In drug combination studies of emtricitabine with nucleoside reverse transcriptase inhibitors (abacavir, lamivudine, stavudine, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Most of these drug combinations have not been studied in humans. Emtricitabine displayed antiviral activity in vitro against HIV-1 clades A, B, C, D, E, F, and G (IC_{50} values ranged from 0.007–0.075 µM) and showed strain specific activity against HIV-2 (IC_{50} values ranged from 0.007–1.5 µM).

Tenofovir disoproxil fumarate: The in vitro antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The IC_{50} (50% inhibitory concentration) values for tenofovir were in the range of 0.04–8.5 µM. In drug combination studies of tenofovir with nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Tenofovir displayed antiviral activity in vitro against HIV-1

clades A, B, C, D, E, F, G and O (IC_{50} values ranged from 0.5–2.2 μM). The IC_{50} values of tenofovir against HIV-2 ranged from 1.6 μM to 4.9 μM.

Resistance

Emtricitabine and tenofovir disoproxil fumarate: HIV-1 isolates with reduced susceptibility to the combination of emtricitabine and tenofovir have been selected in vitro. Genotypic analysis of these isolates identified the M184I/V and/or K65R amino acid substitutions in the viral RT.

Emtricitabine: Emtricitabine-resistant isolates of HIV have been selected in vitro. Genotypic analysis of these isolates showed that the reduced susceptibility to emtricitabine was associated with a mutation in the HIV RT gene at codon 184 which resulted in an amino acid substitution of methionine by valine or isoleucine (M184V/I).

Emtricitabine-resistant isolates of HIV have been recovered from some patients treated with emtricitabine alone or in combination with other antiretroviral agents. In a clinical study, viral isolates from 6/16 (37.5%) treatment-naïve patients with virologic failure showed >20-fold reduced susceptibility to emtricitabine. Genotypic analysis of these isolates showed that the resistance was due to M184V/I mutations in the HIV RT gene.

Tenofovir disoproxil fumarate: HIV-1 isolates with reduced susceptibility to tenofovir have been selected in vitro. These viruses expressed a K65R mutation in RT and showed a 2–4 fold reduction in susceptibility to tenofovir.

Tenofovir-resistant isolates of HIV-1 have also been recovered from some patients treated with VIREAD in combination with certain antiretroviral agents. In treatment-naïve patients, 8/47 (17%) isolates from patients failing VIREAD + lamivudine + efavirenz through week 144 showed >1.4 fold (median 3.7) reduced susceptibility in vitro to tenofovir. In treatment-experienced patients, 14/304 (5%, Studies 902 and 907) isolates from patients failing VIREAD through week 96 showed >1.4 fold (median 2.7) reduced susceptibility to tenofovir. Genotypic analysis of the resistant isolates showed a mutation in the HIV-1 RT gene resulting in the K65R amino acid substitution.

Cross-resistance

Emtricitabine and tenofovir disoproxil fumarate: Cross-resistance among certain nucleoside reverse transcriptase inhibitors (NRTIs) has been recognized. The M184V/I and/or K65R substitutions selected in vitro by the combination of emtricitabine and tenofovir are also observed in some HIV-1 isolates from subjects failing treatment with tenofovir in combination with either lamivudine or emtricitabine, and either abacavir or didanosine. Therefore, cross-resistance among these drugs may occur in patients whose virus harbors either or both of these amino acid substitutions.

Emtricitabine: Emtricitabine-resistant isolates (M184V/I) were cross-resistant to lamivudine and zalcitabine but retained susceptibility in vitro to didanosine, stavudine, tenofovir, zidovudine, and NNRTIs (delavirdine, efavirenz, and nevirapine). Isolates from heavily treatment-experienced patients containing the M184V/I amino acid substitution in the context of other NRTI resistance-associated substitutions may retain susceptibility to tenofovir. HIV-1 isolates containing the K65R substitution, selected in vivo by abacavir, didanosine, tenofovir, and zalcitabine, demonstrated reduced

susceptibility to inhibition by emtricitabine. Viruses harboring mutations conferring reduced susceptibility to stavudine and zidovudine (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) or didanosine (L74V) remained sensitive to emtricitabine. HIV-1 containing the K103N substitution associated with resistance to NNRTIs was susceptible to emtricitabine.

Tenofovir disoproxil fumarate: HIV-1 isolates from patients (N=20) whose HIV-1 expressed a mean of 3 zidovudine-associated RT amino acid substitutions (M41L, D67N, K70R, L210W, T215Y/F or K219Q/E/N) showed a 3.1-fold decrease in the susceptibility to tenofovir. Multinucleoside resistant HIV-1 with a T69S double insertion mutation in the RT showed reduced susceptibility to tenofovir.

CLINICAL PHARMACOLOGY

Pharmacokinetics in Adults

TRUVADA: One TRUVADA Tablet was bioequivalent to one EMTRIVA Capsule (200 mg) plus one VIREAD Tablet (300 mg) following single-dose administration to fasting healthy subjects (N=39).

Emtricitabine: The pharmacokinetic properties of emtricitabine are summarized in Table 1. Following oral administration of EMTRIVA, emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1–2 hours post-dose. In vitro binding of emtricitabine to human plasma proteins is <4% and is independent of concentration over the range of 0.02–200 µg/mL. Following administration of radiolabelled 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. Following a single oral dose of EMTRIVA, the plasma emtricitabine half-life is approximately 10 hours.

Tenofovir disoproxil fumarate: The pharmacokinetic properties of tenofovir disoproxil fumarate are summarized in Table 1. Following oral administration of VIREAD, maximum tenofovir serum concentrations are achieved in 1.0 ± 0.4 hour. In vitro binding of tenofovir to human plasma proteins is <0.7% and 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. Following a single oral dose of VIREAD, the terminal elimination half-life of tenofovir is approximately 17 hours.

Table 1 Single Dose Pharmacokinetic Parameters for Emtricitabine and Tenofovir in Adults[1]

	Emtricitabine	Tenofovir
Fasted Oral Bioavailability[2] (%)	92 (83.1–106.4)	25 (NC–45.0)
Plasma Terminal Elimination Half-Life[2] (hr)	10 (7.4–18.0)	17 (12.0–25.7)
C_{max}[3] (µg/mL)	1.8 ± 0.72[4]	0.30 ± 0.09
AUC[3] (µg·hr/mL)	10.0 ± 3.12[4]	2.29 ± 0.69
CL/F[3] (mL/min)	302 ± 94	1043 ± 115
CL_{renal}[3] (mL/min)	213 ± 89	243 ± 33

1. NC = Not calculated
2. Median (range)
3. Mean (± SD)
4. Data presented as steady state values.

Effects of Food on Oral Absorption

TRUVADA may be administered with or without food. Administration of TRUVADA following a high fat meal (784 kcal; 49 grams of fat) or a light meal (373 kcal; 8 grams of fat) delayed the time of tenofovir C_{max} by approximately 0.75 hour. The mean increases in tenofovir AUC and C_{max} were approximately 35% and 15%, respectively, when administered with a high fat or light meal, compared to administration in the fasted state. In previous safety and efficacy studies, VIREAD (tenofovir) was taken under fed conditions. Emtricitabine systemic exposures (AUC and C_{max}) were unaffected when TRUVADA was administered with either a high fat or a light meal.

Special Populations

Race

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

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

Gender

Emtricitabine and tenofovir disoproxil fumarate: Emtricitabine and tenofovir pharmacokinetics are similar in male and female patients.

Pediatric and Geriatric Patients: Pharmacokinetics of emtricitabine and tenofovir have not been fully evaluated in children (<18 years) or in the elderly (>65 years) **(see PRECAUTIONS, Pediatric Use, Geriatric Use)**.

Patients with Impaired Renal Function: The pharmacokinetics of emtricitabine and tenofovir are altered in patients with renal impairment **(see WARNINGS, Renal Impairment)**. In patients with creatinine clearance <50 mL/min, C_{max}, and $AUC_{0-\infty}$ of emtricitabine and tenofovir were increased. It is recommended that the dosing interval for TRUVADA be modified in patients with creatinine clearance 30–49 mL/min.

TRUVADA should not be used in patients with creatinine clearance <30 mL/min and in patients with end-stage renal disease requiring dialysis **(see WARNINGS, Renal Impairment)**.

Patients with Hepatic Impairment: The pharmacokinetics of tenofovir following a 300 mg dose of VIREAD have been studied in non-HIV infected patients with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in patients with hepatic impairment compared with unimpaired patients. The pharmacokinetics of TRUVADA or emtricitabine have not been studied in patients with hepatic impairment; however, emtricitabine is not significantly metabolized by liver enzymes, so the impact of liver impairment should be limited.

Pregnancy: (see PRECAUTIONS, Pregnancy)

Nursing Mothers: (see PRECAUTIONS, Nursing Mothers)

Drug Interactions: (see PRECAUTIONS, Drug Interactions)

TRUVADA: No drug interaction studies have been conducted using TRUVADA Tablets.

Emtricitabine and tenofovir disoproxil fumarate: The steady state pharmacokinetics of emtricitabine and tenofovir were unaffected when emtricitabine and tenofovir disoproxil fumarate were administered together versus each agent dosed alone.

In vitro and clinical pharmacokinetic drug-drug interaction studies have shown the potential for CYP450 mediated interactions involving emtricitabine and tenofovir with other medicinal products is low.

Emtricitabine and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. No drug-drug interactions due to competition for renal excretion have been observed; however, coadministration of TRUVADA with drugs that are eliminated by active tubular secretion may increase concentrations of emtricitabine, tenofovir, and/or the coadministered drug.

Drugs that decrease renal function may increase concentrations of emtricitabine and/or tenofovir.

No clinically significant drug interactions have been observed between emtricitabine and famciclovir, indinavir, stavudine, and tenofovir disoproxil fumarate (see Tables 2 and 3). Similarly, no clinically significant drug interactions have been observed between tenofovir disoproxil fumarate and abacavir, adefovir dipivoxil, ribavirin, efavirenz, emtricitabine, indinavir, lamivudine, lopinavir/ritonavir, methadone and oral contraceptives in studies conducted in healthy volunteers (see Tables 4 and 5).

Table 2 Drug Interactions: Changes in Pharmacokinetic Parameters for Emtricitabine in the Presence of the Coadministered Drug[1]

Coadministered Drug	Dose of Coadministered Drug (mg)	Emtricitabine Dose (mg)	N	% Change of Emtricitabine Pharmacokinetic Parameters[2] (90% CI)		
				C_{max}	AUC	C_{min}
Tenofovir DF	300 once daily x 7 days	200 once daily x 7 days	17	⇔	⇔	↑ 20 (↑ 12 to ↑ 29)
Indinavir	800 x 1	200 x 1	12	⇔	⇔	NA
Famciclovir	500 x 1	200 x 1	12	⇔	⇔	NA
Stavudine	40 x 1	200 x 1	6	⇔	⇔	NA

1. All interaction studies conducted in healthy volunteers.
2. ↑ = Increase; ↓ = Decrease; ⇔ = No Effect; NA = Not Applicable

Table 3 Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Emtricitabine[1]

Coadministered Drug	Dose of Coadministered Drug (mg)	Emtricitabine Dose (mg)	N	% Change of Coadministered Drug Pharmacokinetic Parameters[2] (90% CI)		
				C_{max}	AUC	C_{min}
Tenofovir DF	300 once daily x 7 days	200 once daily x 7 days	17	⇔	⇔	⇔
Indinavir	800 x 1	200 x 1	12	⇔	⇔	NA
Famciclovir	500 x 1	200 x 1	12	⇔	⇔	NA
Stavudine	40 x 1	200 x 1	6	⇔	⇔	NA

1. All interaction studies conducted in healthy volunteers.
2. ↑ = Increase; ↓ = Decrease; ⇔ = No Effect; NA = Not Applicable

Table 4 Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir[1] in the Presence of the Coadministered Drug

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Tenofovir Pharmacokinetic Parameters[2] (90% CI)		
			C_{max}	AUC	C_{min}
Abacavir	300 once	8	⇔	⇔	NC
Adefovir dipivoxil	10 once	22	⇔	⇔	NC
Atazanavir[3]	400 once daily x 14 days	33	↑ 14 (↑ 8 to ↑ 20)	↑ 24 (↑ 21 to ↑ 28)	↑ 22 (↑ 15 to ↑ 30)
Didanosine (enteric-coated)	400 once	25	⇔	⇔	⇔
Didanosine (buffered)	250 or 400 once daily x 7 days	14	⇔	⇔	⇔
Efavirenz	600 once daily x 14 days	29	⇔	⇔	⇔
Emtricitabine	200 once daily x 7 days	17	⇔	⇔	⇔
Indinavir	800 three times daily x 7 days	13	↑ 14 (↓ 3 to ↑ 33)	⇔	⇔
Lamivudine	150 twice daily x 7 days	15	⇔	⇔	⇔
Lopinavir/ Ritonavir	400/100 twice daily x 14 days	24	⇔	↑ 32 (↑ 25 to ↑ 38)	↑ 51 (↑ 37 to ↑ 66)

1. Patients received VIREAD 300 mg once daily.
2. Increase = ↑; Decrease = ↓; No Effect = ⇔; NC = Not Calculated
3. REYATAZ® Prescribing Information (Bristol-Myers Squibb)

Table 5 Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Tenofovir

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Coadministered Drug Pharmacokinetic Parameters[1] (90% CI)		
			C_{max}	AUC	C_{min}
Abacavir	300 once	8	↑ 12 (↓ 1 to ↑ 26)	⇔	NA
Adefovir dipivoxil	10 once	22	⇔	⇔	NA
Atazanavir[2]	400 once daily x 14 days	34	↓ 21 (↓ 27 to ↓ 14)	↓ 25 (↓ 30 to ↓ 19)	↓ 40 (↓ 48 to ↓ 32)
Atazanavir[2]	Atazanavir/Ritonavir 300/100 once daily x 42 days	10	↓ 28 (↓ 50 to ↑ 5)	↓ 25[3] (↓ 42 to ↓ 3)	↓ 23[3] (↓ 46 to ↑ 10)
Efavirenz	600 once daily x 14 days	30	⇔	⇔	⇔
Emtricitabine	200 once daily x 7 days	17	⇔	⇔	↑ 20 (↑ 12 to ↑ 29)
Indinavir	800 three times daily x 7 days	12	↓ 11 (↓ 30 to ↑ 12)	⇔	⇔
Lamivudine	150 twice daily x 7 days	15	↓ 24 (↓ 34 to ↓ 12)	⇔	⇔
Lopinavir	Lopinavir/Ritonavir 400/100 twice daily x 14 days	24	⇔	⇔	⇔
Methadone[4]	40-110 once daily x 14 days[5]	13	⇔	⇔	⇔
Oral Contraceptives[6]	Ethinyl Estradiol/ Norgestimate (Ortho-Tricyclen®) Once daily x 7 days	20	⇔	⇔	⇔
Ribavirin	600 once	22	⇔	⇔	NA
Ritonavir	Lopinavir/Ritonavir 400/100 twice daily x 14 days	24	⇔	⇔	⇔

1. Increase = ↑; Decrease = ↓; No Effect = ⇔; NA = Not Applicable
2. REYATAZ Prescribing Information (Bristol-Myers Squibb)
3. In HIV-infected patients, addition of tenofovir DF to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and C_{min} values of atazanavir that were 2.3 and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone.
4. R-(active), S-and total methadone exposures were equivalent when dosed alone or with VIREAD.
5. Individual subjects were maintained on their stable methadone dose. No pharmacodynamic alterations (opiate toxicity or withdrawal signs or symptoms) were reported.
6. Ethinyl estradiol and 17-deacetyl norgestimate (pharmacologically active metabolite) exposures were equivalent when dosed alone or with VIREAD.

Following multiple dosing to HIV-negative subjects receiving either chronic methadone maintenance therapy or oral contraceptives, or single doses of ribavirin, steady state tenofovir pharmacokinetics were similar to those observed in previous studies, indicating lack of clinically significant drug interactions between these agents and VIREAD.

Coadministration of tenofovir disoproxil fumarate with didanosine results in changes in the pharmacokinetics of didanosine that may be of clinical significance. Table 6 summarizes the effects of tenofovir disoproxil fumarate on the pharmacokinetics of didanosine. Concomitant dosing of tenofovir disoproxil fumarate with didanosine buffered tablets or enteric-coated capsules significantly increases the C_{max} and AUC of didanosine. When didanosine 250 mg enteric-coated capsules were administered with tenofovir disoproxil fumarate, systemic exposures of didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions. The mechanism of this interaction is unknown.

Table 6 Drug Interactions: Pharmacokinetic Parameters for Didanosine in the Presence of VIREAD

Didanosine[1] Dose (mg)/ Method of Administration[2]	VIREAD Method of Administration[2]	N	% Difference (90% CI) vs. Didanosine 400 mg Alone, Fasted[3]	
			C_{max}	AUC
Buffered tablets				
400 once daily[4] x 7 days	Fasted 1 hour after didanosine	14	↑ 28 (↑ 11 to ↑ 48)	↑ 44 (↑ 31 to ↑ 59)
Enteric coated capsules				
400 once, fasted	With food, 2 hr after didanosine	26	↑ 48 (↑ 25 to ↑ 76)	↑ 48 (↑ 31 to ↑ 67)
400 once, with food	Simultaneously with didanosine	26	↑ 64 (↑ 41 to ↑ 89)	↑ 60 (↑ 44 to ↑ 79)
250 once, fasted	With food, 2 hr after didanosine	28	↓ 10 (↓ 22 to ↑ 3)	⇔
250 once, fasted	Simultaneously with didanosine	28	⇔	↑ 14 (0 to ↑ 31)
250 once, with food	Simultaneously with didanosine	28	↓ 29 (↓ 39 to ↓ 18)	↓ 11 (↓ 23 to ↑ 2)

1. See PRECAUTIONS regarding use of didanosine with VIREAD.
2. Administration with food was with a light meal (~373 kcal, 20% fat).
3. Increase = ↑; Decrease = ↓; No Difference = ⇔
4. Includes 4 subjects weighing <60 kg receiving ddI 250 mg.

INDICATIONS AND USAGE

TRUVADA is indicated in combination with other antiretroviral agents (such as non-nucleoside reverse transcriptase inhibitors or protease inhibitors) for the treatment of HIV-1 infection in adults. Safety and efficacy studies using TRUVADA Tablets or using EMTRIVA and VIREAD in combination are ongoing.

EMTRIVA and VIREAD have each been studied as part of multidrug regimens and have been found to be safe and effective. In clinical study 303 EMTRIVA and lamivudine (3TC) demonstrated comparable efficacy, safety and resistance patterns as part of multidrug regimens. These data, and those from study 903, in which lamivudine and tenofovir were used in combination, support the use of TRUVADA Tablets for the treatment of HIV-1 infection in treatment-naïve adults **(see Description of Clinical Studies and Adverse Events)**. In treatment experienced patients, the use of TRUVADA should be guided by laboratory testing and treatment history **(see Microbiology)**.

Additional important information regarding the use of TRUVADA for the treatment of HIV-1 infection:

- There are no study results demonstrating the effect of TRUVADA on clinical progression of HIV-1.
- It is not recommended that TRUVADA be used as a component of a triple nucleoside regimen.

Description of Clinical Studies

For safety and efficacy studies using EMTRIVA or VIREAD in combination with other antiretroviral agents, also consult the Prescribing Information for these products.

Safety and efficacy studies using TRUVADA Tablets or using EMTRIVA and VIREAD in combination are ongoing.

EMTRIVA:

Study 303: EMTRIVA QD + Stable Background Therapy (SBT) Compared to Lamivudine BID + SBT

Study 303 was a 48 week, open-label, active-controlled multicenter study comparing EMTRIVA (200 mg QD) to lamivudine, in combination with stavudine or zidovudine and a protease inhibitor or NNRTI in 440 patients who were on a lamivudine-containing triple-antiretroviral drug regimen for at least 12 weeks prior to study entry and had HIV-1 RNA ≤400 copies/mL.

Patients were randomized 1:2 to continue therapy with lamivudine (150 mg BID) or to switch to EMTRIVA (200 mg QD). All patients were maintained on their stable background regimen. Patients had a mean age of 42 years (range 22–80), 86% were male, 64% Caucasian, 21% African-American and 13% Hispanic. Patients had a mean baseline CD4 cell count of 527 cells/mm^3 (range 37–1909), and a median baseline plasma HIV RNA of 1.7 $\log_{10}$ copies/mL (range 1.7–4.0). The median duration of prior antiretroviral therapy was 27.6 months. Treatment outcomes through 48 weeks are presented in Table 7.

Table 7 Outcomes of Randomized Treatment at Week 48 (Study 303)

Outcome at Week 48	EMTRIVA + ZDV/d4T + NNRTI/PI (N=294)	Lamivudine + ZDV/d4T + NNRTI/PI (N=146)
Responder[1]	77% (67%)	82% (72%)
Virologic Failure[2]	7%	8%
Death	0%	<1%
Study Discontinuation Due to Adverse Event	4%	0%
Study Discontinuation For Other Reasons[3]	12%	10%

1. Patients achieved and maintained confirmed HIV RNA <400 copies/mL (<50 copies/mL) through week 48.
2. Includes patients who failed to achieve virologic suppression or rebounded after achieving virologic suppression.
3. Includes lost to follow-up, patient withdrawal, non-compliance, protocol violation and other reasons.

The mean increase from baseline in CD4 cell count was 29 cells/mm^3 for the EMTRIVA arm and 61 cells/mm^3 for the lamivudine arm. Through 48 weeks, in the EMTRIVA group 2 patients (0.7%) experienced a new CDC Class C event, compared to 2 patients (1.4%) in the lamivudine group.

VIREAD:

Study 903: VIREAD + Lamivudine + Efavirenz Compared with Stavudine + Lamivudine + Efavirenz

Data through 144 weeks are reported for Study 903, a double-blind, active-controlled multicenter study comparing VIREAD (300 mg QD) administered in combination with lamivudine and efavirenz versus stavudine, lamivudine, and efavirenz in 600 antiretroviral-naïve patients. Patients had a mean age of 36 years (range 18–64), 74% were male, 64% were Caucasian and 20% were Black. The mean baseline CD4 cell count was 279 cells/mm^3 (range 3–956) and median baseline plasma HIV-1 RNA was 77,600 copies/mL (range 417–5,130,000). Patients were stratified by baseline HIV-1 RNA and CD4 count. Forty-three percent of patients had baseline viral loads >100,000 copies/mL and 39% had CD4 cell counts <200 cells/mm^3. Treatment outcomes through 144 weeks are presented in Table 8.

Table 8 Outcomes of Randomized Treatment (Study 903)

Outcomes	At Week 48		At Week 144	
	VIREAD+3TC +EFV (N=299)	Stavudine+ 3TC+EFV (N=301)	VIREAD+3TC +EFV (N=299)	Stavudine+ 3TC+EFV (N=301)
	%	%	%	%
Responder[1]	79%	82%	68%	62%
Virologic failure[2]	6%	4%	10%	8%
Rebound	5%	3%	8%	7%
Never suppressed	0%	1%	0%	0%
Added an antiretroviral agent	1%	1%	2%	1%
Death	<1%	1%	<1%	2%
Discontinued due to adverse event	6%	6%	8%	13%
Discontinued for other reasons[3]	8%	7%	14%	15%

1. Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Week 48 and 144.
2. Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Week 48 and 144.
3. Includes lost to follow-up, patient's withdrawal, noncompliance, protocol violation and other reasons.

Achievement of plasma HIV-1 RNA concentrations of less than 400 copies/mL at week 144 was similar between the two treatment groups for the population stratified at baseline on the basis of HIV-1 RNA concentration (> or ≤ 100,000 copies/mL) and CD4 cell count (< or ≥ 200 cells/mm^3). Through 144 weeks of therapy, 62% and 58% of patients in the VIREAD and stavudine arms, respectively achieved and maintained confirmed HIV-1 RNA <50 copies/mL. The mean increase from baseline in CD4 cell count was 263 cells/mm^3 for the VIREAD arm and 283 cells/mm^3 for the stavudine arm.

Through 144 weeks, eleven patients in the VIREAD group and nine patients in the stavudine group experienced a new CDC Class C event.

Genotypic analyses of patients with virologic failure showed development of efavirenz-associated and lamivudine-associated mutations to occur most frequently and with no difference between the treatment arms. The K65R mutation occurred in 8 patients on the VIREAD arm and in 2 patients on the stavudine arm. Of the 8 patients who developed K65R in the VIREAD arm through 144 weeks, 7 of these occurred in the first 48 weeks of treatment and one at week 96. Other mutations resulting in resistance to VIREAD were not identified in this study.

CONTRAINDICATIONS

TRUVADA is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the product.

WARNINGS

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination 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 TRUVADA should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Patients with HIV and Hepatitis B Virus Coinfection

It is recommended that all patients with HIV be tested for the presence of hepatitis B virus (HBV) before initiating antiretroviral therapy. TRUVADA is not indicated for the treatment of chronic HBV infection and the safety and efficacy of TRUVADA have not been established in patients coinfected with HBV and HIV. Severe acute exacerbations of hepatitis B have been reported in patients after the discontinuation of EMTRIVA and VIREAD. Hepatic function should be closely monitored with both clinical and laboratory follow up for at least several months in patients who discontinue TRUVADA and are coinfected with HIV and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

Renal Impairment

Emtricitabine and tenofovir are principally eliminated by the kidney. Dosing interval adjustment of TRUVADA is recommended in all patients with creatinine clearance 30–49 mL/min, **(see DOSAGE AND ADMINISTRATION)**. TRUVADA should not be administered to patients with creatine clearance <30 mL/min or patients requiring hemodialysis.

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported in association with the use of VIREAD **(see ADVERSE REACTIONS-Post Marketing Experience)**. The majority of these cases occurred in patients with underlying systemic or renal disease, or in patients taking nephrotoxic agents, however, some cases occurred in patients without identified risk factors.

TRUVADA should be avoided with concurrent or recent use of a nephrotoxic agent. Patients at risk for, or with a history of, renal dysfunction and patients receiving concomitant nephrotoxic agents should be carefully monitored for changes in serum creatinine and phosphorus.

PRECAUTIONS

Drug Interactions

Tenofovir disoproxil fumarate: When tenofovir disoproxil fumarate was administered with didanosine the C_{max} and AUC of didanosine administered as either the buffered or enteric-coated formulation increased significantly (see Table 6). The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse events, including pancreatitis, and neuropathy. In adults weighing >60 kg, the didanosine dose should be reduced to 250 mg when it is coadministered with TRUVADA. Data are not available to recommend a dose adjustment of didanosine for patients weighing <60 kg. When coadministered, TRUVADA and VIDEX EC® may be taken under fasted conditions or with a light meal (<400 kcal, 20% fat). Coadministration of didanosine buffered tablet formulation with TRUVADA should be under fasted conditions. **Coadministration of TRUVADA and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse events. Didanosine should be discontinued in patients who develop didanosine-associated adverse events.**

Atazanavir and lopinavir/ritonavir have been shown to increase tenofovir concentrations. The mechanism of this interaction is unknown. **Patients receiving atazanavir and lopinavir/ritonavir and TRUVADA should be monitored for TRUVADA-associated adverse events. TRUVADA should be discontinued in patients who develop TRUVADA-associated adverse events.**

Tenofovir decreases the AUC and C_{min} of atazanavir. When coadministered with TRUVADA, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. **Atazanavir without ritonavir should not be coadministered with TRUVADA.**

Emtricitabine and tenofovir disoproxil fumarate: Since emtricitabine and tenofovir are primarily eliminated by the kidneys, coadministration of TRUVADA 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 adefovir dipivoxil, cidofovir, acyclovir, valacyclovir, ganciclovir and valganciclovir.

TRUVADA is a fixed-dose combination of emtricitabine and tenofovir disoproxil fumarate. TRUVADA should not be coadministered with EMTRIVA or VIREAD. Due to similarities between emtricitabine and lamivudine, TRUVADA should not be coadministered with other drugs containing lamivudine, including COMBIVIR®, EPIVIR, EPIVIR-HBV®, EPZICOM™, or TRIZIVIR®.

Bone Effects

Tenofovir disoproxil fumarate: In study 903 through 144 weeks, decreases from baseline in bone mineral density (BMD) were seen at the lumbar spine and hip in both arms of the study. At week 144, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in patients receiving VIREAD + lamivudine + efavirenz (-2.2% ± 3.9) compared with patients receiving stavudine + lamivudine + efavirenz (-1.0% ± 4.6). Changes in BMD at the hip were similar between the two treatment groups (-2.8% ± 3.5 in the VIREAD group vs. -2.4% ± 4.5 in the stavudine group). In both groups, the majority of the reduction in BMD occurred in the first 24-48 weeks of the study and this reduction was sustained through week 144. Twenty-eight percent of VIREAD-treated patients vs. 21% of the stavudine-treated patients lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 patients in the VIREAD group and 6 patients in the stavudine group. In addition, there were significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide and urinary N-telopeptide) in the VIREAD group relative to the stavudine group, suggesting increased bone turnover. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in the VIREAD group relative to the stavudine group. Except for bone specific alkaline phosphatase, these changes resulted in values that remained within the normal range. The effects of VIREAD-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown.

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

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.

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including VIREAD. 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.

Information for Patients

TRUVADA is not a cure for HIV infection and patients may continue to experience illnesses associated with HIV infection, including opportunistic infections. Patients should remain under the care of a physician when using TRUVADA.

- Patients should be advised that:
- the use of TRUVADA has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination,
- the long term effects of TRUVADA are unknown,
- TRUVADA Tablets are for oral ingestion only,
- it is important to take TRUVADA with combination therapy on a regular dosing schedule to avoid missing doses,
- redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known.
- TRUVADA should not be coadministered with EMTRIVA or VIREAD, or drugs containing lamivudine, including COMBIVIR, EPIVIR, EPIVIR-HBV, EPZICOM, or TRIZIVIR.

Animal Toxicology

Tenofovir and tenofovir disoproxil fumarate 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. 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) 2–20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia, to the bone toxicity is not known.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Emtricitabine: Long-term carcinogenicity studies of emtricitabine in rats and mice are in progress.

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 disoproxil fumarate 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 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 disoproxil fumarate 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 disoproxil fumarate was negative when administered to male mice.

There were no effects on fertility, mating performance or early embryonic development when tenofovir disoproxil fumarate 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.

Pregnancy

Pregnancy Category B:

Emtricitabine: The incidence of fetal variations and malformations was not increased in embryofetal toxicity studies performed with emtricitabine in mice at exposures (AUC) approximately 60-fold higher and in rabbits at approximately 120-fold higher than human exposures at the recommended daily dose.

Tenofovir disoproxil fumarate: Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, TRUVADA should be used during pregnancy only if clearly needed.

Antiretroviral Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to TRUVADA, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients by calling 1-800-258-4263.

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of EMTRIVA or VIREAD did not include sufficient numbers of subjects aged 65 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.

ADVERSE REACTIONS

Clinical Trials

TRUVADA: Safety and efficacy studies using TRUVADA Tablets or using EMTRIVA and VIREAD in combination are ongoing. Two hundred eighty three HIV-1 infected patients have received combination therapy with EMTRIVA and VIREAD with either a non-nucleoside reverse transcriptase inhibitor or protease inhibitor for 24 to 48 weeks in ongoing clinical studies. Based on these limited data, no new patterns of adverse events were identified and there was no increased frequency of established toxicities.

For additional safety information about EMTRIVA or VIREAD in combination with other antiretroviral agents, also consult the Prescribing Information for these products.

EMTRIVA: Adverse events that occurred in >5% of patients receiving EMTRIVA with other antiretroviral agents in clinical trials include abdominal pain, asthenia, headache, diarrhea, nausea, vomiting, dizziness, and rash event (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash and allergic reaction). Approximately 1% of patients discontinued participation in the clinical studies because of these adverse events.

Other adverse events reported include dyspepsia, arthralgia, myalgia, abnormal dreams, depressive disorder, insomnia, neuropathy, peripheral neuritis, paresthesia, increased cough, and rhinitis.

All adverse events were reported with similar frequency in EMTRIVA and control treatment groups with the exception of skin discoloration which was reported with higher frequency in the EMTRIVA treated group. Skin discoloration, manifested by hyperpigmentation on the palms and/or soles was generally mild and asymptomatic. The mechanism and clinical significance are unknown.

Grade 3/4 elevations of ALT and AST (>5 x ULN), bilirubin (>2.5 x ULN), creatine kinase (>4 x ULN), decreased neutrophils (<750/mm^3), pancreatic amylase (>2.0 x ULN), serum amylase (>2 x ULN), serum glucose (<40 or >250 mg/dL), serum lipase (>2.0 x ULN) and triglycerides (>750 mg/dL) have been reported to occur in 1–12% of patients receiving EMTRIVA.

VIREAD: Adverse events that occurred in >5% of patients receiving VIREAD with other antiretroviral agents in clinical trials included: headache, nausea, diarrhea, vomiting, rash event (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash), and depression. Less than 1% of patients discontinued participation in the clinical studies because of gastrointestinal adverse events.

Other adverse events include asthenia, pain, abdominal pain, back pain, chest pain, fever, flatulence, dizziness, dyspepsia, anorexia, arthralgia, lipodystrophy, insomnia, peripheral neuropathy (including peripheral neuritis and neuropathy), anxiety, pneumonia, sweating, myalgia and weight loss.

Grade 3/4 elevations of ALT and AST (>5 x ULN), creatine kinase (>4 x ULN), serum amylase (>2 x ULN), urine glucose (≥3+), serum glucose (>250 mg/dL) and serum triglycerides (>750 mg/dL), hematuria (>100 RBC/HPF), total cholesterol (> 300 mg/dL), and decreased neutrophils (<750/mm^3) have been reported to occur in 2–12% of patients receiving VIREAD.

Post Marketing Experience

EMTRIVA: No additional events have been identified for inclusion in this section.

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

IMMUNE SYSTEM DISORDERS
Allergic reaction

METABOLISM AND NUTRITION DISORDERS
Hypophosphatemia, Lactic acidosis

RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS
Dyspnea

GASTROINTESTINAL DISORDERS
Abdominal pain, Increased amylase, Pancreatitis

HEPATOBILIARY DISORDERS
Increased liver enzymes, Hepatitis

RENAL AND URINARY DISORDERS
Renal insufficiency, Renal failure, Acute renal failure, Fanconi syndrome, Proximal tubulopathy, Proteinuria, Increased creatinine, Acute tubular necrosis, Nephrogenic diabetes insipidus

OVERDOSAGE

If overdose occurs the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.

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

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

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

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

DOSAGE AND ADMINISTRATION

The dose of TRUVADA is one tablet (containing 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate) once daily taken orally with or without food.

Dose Adjustment for Renal Impairment:

Significantly increased drug exposures occurred when EMTRIVA or VIREAD were administered to patients with moderate to severe renal impairment **(see EMTRIVA or VIREAD Package Insert)**. Therefore, the dosing interval of TRUVADA should be adjusted in patients with baseline creatinine clearance 30–49 mL/min using the recommendations in Table 9. The safety and effectiveness of these dosing interval adjustment recommendations have not been clinically evaluated, therefore, clinical response to treatment and renal function should be closely monitored in these patients.

Table 9 Dosage Adjustment for Patients with Altered Creatinine Clearance

	Creatinine Clearance (mL/min)[a]		
	≥50	**30–49**	**<30 (Including Patients Requiring Hemodialysis)**
Recommended Dosing Interval	Every 24 hours	Every 48 hours	TRUVADA should not be administered.

[a] Calculated using ideal (lean) body weight

HOW SUPPLIED

TRUVADA is available as tablets. Each tablet contains 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate (which is equivalent to 245 mg of tenofovir disoproxil). The tablets are blue, capsule-shaped, film-coated, debossed with "GILEAD" on one side and with "701" on the other side. Each bottle contains 30 tablets (NDC 61958-0701-1) and a desiccant (silica gel canister or sachet) and is closed with a child-resistant closure.

Store at 25 °C (77 °F), excursions permitted to 15–30 °C (59–86 °F).

- Keep container tightly closed
- Dispense only in original container
- Do not use if seal over bottle opening is broken or missing.

Gilead Sciences, Inc.
Foster City, CA 94404

May 2005

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21-752-GS18

Patient Information
TRUVADA® (tru-vah-dah) Tablets

Generic name: emtricitabine and tenofovir disoproxil fumarate
(em tri SIT uh bean and te NOE' fo veer dye soe PROX il FYOU-mar-ate)

Read the Patient Information that comes with TRUVADA before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment. You should stay under a healthcare provider's care when taking TRUVADA. **Do not change or stop your medicine without first talking with your healthcare provider**. Talk to your healthcare provider or pharmacist if you have any questions about TRUVADA.

What is the most important information I should know about TRUVADA?

- **Some people who have taken medicine like TRUVADA (nucleoside analogs) have developed a serious condition called lactic acidosis** (build up of an acid in the blood). Lactic acidosis can be a medical emergency and may need to be treated in the hospital. **Call your healthcare provider right away if you get the following signs or symptoms of lactic acidosis.**
  - You feel very weak or tired.
  - You have unusual (not normal) muscle pain.
  - You have trouble breathing.
  - You have stomach pain with nausea and vomiting.
  - You feel cold, especially in your arms and legs.
  - You feel dizzy or lightheaded.
  - You have a fast or irregular heartbeat.
- **Some people who have taken medicines like TRUVADA have developed serious liver problems called hepatotoxicity**, with liver enlargement (hepatomegaly) and fat in the liver (steatosis). **Call your healthcare provider right away if you get the following signs or symptoms of liver problems.**
  - Your skin or the white part of your eyes turns yellow (jaundice).
  - Your urine turns dark.
  - Your bowel movements (stools) turn light in color.
  - You don't feel like eating food for several days or longer.
  - You feel sick to your stomach (nausea).
  - You have lower stomach area (abdominal) pain.
- **You may be more likely to get lactic acidosis or liver problems** if you are female, very overweight (obese), or have been taking nucleoside analog medicines, like TRUVADA, for a long time.
- **TRUVADA is not for the treatment of Hepatitis B Virus infection**. Patients infected with both HBV and human immunodeficiency virus (HIV) who take

TRUVADA need close medical follow-up for several months after stopping treatment with TRUVADA. Follow-up includes medical exams and blood tests to check for HBV that could be getting worse. **Patients with Hepatitis B Virus infection, who take TRUVADA and then stop it, may get "flare-ups" of their hepatitis. A "flare-up" is when the disease suddenly returns in a worse way than before.**

What is TRUVADA?

TRUVADA is a type of medicine called an HIV (human immunodeficiency virus) nucleoside analog reverse transcriptase inhibitor (NRTI). TRUVADA contains 2 medicines, EMTRIVA® (emtricitabine) and VIREAD® (tenofovir disoproxil fumarate, or tenofovir DF) combined in one pill. TRUVADA is always used with other anti-HIV medicines to treat people with HIV infection. TRUVADA is for adults age 18 and older. TRUVADA has not been studied in children under age 18 or adults over age 65.

HIV infection destroys CD4 (T) cells, which are important to the immune system. The immune system helps fight infection. After a large number of T cells are destroyed, acquired immune deficiency syndrome (AIDS) develops.

TRUVADA helps block HIV reverse transcriptase, a chemical in your body (enzyme) that is needed for HIV to multiply. TRUVADA lowers the amount of HIV in the blood (viral load). TRUVADA may also help to increase the number of T cells (CD4 cells). Lowering the amount of HIV in the blood lowers the chance of death or infections that happen when your immune system is weak (opportunistic infections).

TRUVADA does not cure HIV infection or AIDS. The long-term effects of TRUVADA are not known at this time. People taking TRUVADA may still get opportunistic infections or other conditions that happen with HIV infection. Opportunistic infections are infections that develop because the immune system is weak. Some of these conditions are pneumonia, herpes virus infections, and *Mycobacterium avium complex* (MAC) infection. **It is very important that you see your healthcare provider regularly while taking TRUVADA.**

TRUVADA does not lower your chance of passing HIV to other people through sexual contact, sharing needles, or being exposed to your blood. For your health and the health of others, it is important to always practice safer sex by using a latex or polyurethane condom or other barrier to lower the chance of sexual contact with semen, vaginal secretions, or blood. Never use or share dirty needles.

Who should not take TRUVADA?

Do not take TRUVADA if you are allergic to TRUVADA or any of its ingredients. The active ingredients of TRUVADA are emtricitabine and tenofovir DF. See the end of this leaflet for a complete list of ingredients.

What should I tell my healthcare provider before taking TRUVADA?

Tell your healthcare provider if you:

- **are pregnant or planning to become pregnant.** We do not know if TRUVADA can harm your unborn child. You and your healthcare provider will need to decide if TRUVADA is right for you. If you use TRUVADA while you are pregnant, talk to your

healthcare provider about how you can be on the TRUVADA Antiviral Pregnancy Registry.

- **are breast-feeding.** You should not breast feed if you are HIV-positive because of the chance of passing the HIV virus to your baby. Also, it is not known if TRUVADA can pass into your breast milk and if it can harm your baby. If you are a woman who has or will have a baby, talk with your healthcare provider about the best way to feed your baby.
- **have kidney problems or are undergoing kidney dialysis treatment.**
  - **have bone problems.**
  - **have liver problems including Hepatitis B Virus infection.**

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Especially tell your healthcare provider if you take:

- COMBIVIR®, EMTRIVA, EPIVIR®, EPIVIR-HBV®, EPZICOM™, TRIZIVIR®, or VIREAD. **TRUVADA should not be used with those medicines.**
- Drugs that contain didanosine (VIDEX®, VIDEX EC®). Tenofovir DF (a component of TRUVADA) may increase the amount of VIDEX in your blood. **You may need to be followed more carefully if you are taking TRUVADA and VIDEX together.**
- REYATAZ™ (atazanavir sulfate) or KALETRA® (lopinavir/ritonavir). These medicines may increase the amount of tenofovir DF (a component of TRUVADA) in your blood, which could result in more side effects. You may need to be followed more carefully if you are taking TRUVADA and REYATAZ or KALETRA together.

Keep a complete list of all the medicines that you take. Make a new list when medicines are added or stopped. Give copies of this list to all of your healthcare providers and pharmacist **every** time you visit your healthcare provider or fill a prescription.

How should I take TRUVADA?

- Take TRUVADA exactly as your healthcare provider prescribed it. Follow the directions from your healthcare provider, exactly as written on the label.
- The usual dose of TRUVADA is 1 tablet once a day. TRUVADA is always used with other anti-HIV medicines. If you have kidney problems, you may need to take TRUVADA less often.
- TRUVADA may be taken with or without a meal. Food does not affect how TRUVADA works. Take TRUVADA at the same time each day.
- If you forget to take TRUVADA, take it as soon as you remember that day. **Do not** take more than 1 dose of TRUVADA in a day. **Do not** take 2 doses at the same time. Call your healthcare provider or pharmacist if you are not sure what to do. **It is important that you do not miss any doses of TRUVADA or your anti-HIV medicines.**

- When your TRUVADA supply starts to run low, get more from your healthcare provider or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short time. The virus may develop resistance to TRUVADA and become harder to treat.
- Do not change your dose or stop taking TRUVADA without first talking with your healthcare provider. Stay under a healthcare provider's care when taking TRUVADA.
- If you take too much TRUVADA, call your local poison control center or emergency room right away.

What should I avoid while taking TRUVADA?

- **Do not breast-feed.** See "What should I tell my healthcare provider before taking TRUVADA?"
- **Avoid doing things that can spread HIV infection** since TRUVADA does not stop you from passing the HIV infection to others.
  - **Do not share needles or other injection equipment.**
  - **Do not share personal items that can have blood or body fluids on them, like toothbrushes or razor blades.**
  - **Do not have any kind of sex without protection.** Always practice safer sex by using a latex or polyurethane condom or other barrier to reduce the chance of sexual contact with semen, vaginal secretions, or blood.
- COMBIVIR, EMTRIVA, EPIVIR, EPIVIR-HBV, EPZICOM, TRIZIVIR, or VIREAD. **TRUVADA should not be used with these medicines.**

What are the possible side effects of TRUVADA?

TRUVADA may cause the following serious side effects (see "What is the most important information I should know about TRUVADA?"):

- **Lactic acidosis** (buildup of an acid in the blood). Lactic acidosis can be a medical emergency and may need to be treated in the hospital. **Call your doctor right away if you get signs of lactic acidosis.** (See "What is the most important information I should know about TRUVADA?")
- **Serious liver problems (hepatotoxicity),** with liver enlargement (hepatomegaly) and fat in the liver (steatosis). Call your healthcare provider right away if you get any signs of liver problems. (See "What is the most important information I should know about TRUVADA?")
- **"Flare-ups" of Hepatitis B Virus infection,** in which the disease suddenly returns in a worse way than before, can occur if you stop taking TRUVADA. Your healthcare provider will monitor your condition for several months after stopping TRUVADA if you have both HIV and HBV infection. TRUVADA is not for the treatment of Hepatitis B Virus infection.

- **Kidney problems** If you have had kidney problems in the past or take other medicines that can cause kidney problems, your healthcare provider should do regular blood tests to check your kidneys.
- **Changes in bone mineral density (thinning bones)** It is not known whether long-term use of TRUVADA will cause damage to your bones. If you have had bone problems in the past, your healthcare provider may need to do tests to check your bone mineral density or may prescribe medicines to help your bone mineral density.

Other side effects with TRUVADA when used with other anti-HIV medicines include:

- Changes in body fat have been seen in some patients taking TRUVADA and other anti-HIV medicines. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the main part of your body (trunk). Loss of fat from the legs, arms and face may also happen. The cause and long term health effect of these conditions are not known at this time.

The most common side effects of EMTRIVA or VIREAD when used with other anti-HIV medicines are: dizziness, diarrhea, nausea, vomiting, headache, rash, and gas. Skin discoloration (small spots or freckles) may also happen with TRUVADA.

These are not all the side effects of TRUVADA. This list of side effects with TRUVADA is **not complete** at this time because TRUVADA is still being studied. If you have questions about side effects, ask your healthcare provider. Report any new or continuing symptoms to your healthcare provider right away. Your healthcare provider may be able to help you manage these side effects.

How do I store TRUVADA?

- **Keep TRUVADA and all other medicines out of reach of children.**
- Store TRUVADA at room temperature 77 °F (25 °C).
- Keep TRUVADA in its original container and keep the container tightly closed.
- Do not keep medicine that is out of date or that you no longer need. If you throw any medicines away make sure that children will not find them.

General information about TRUVADA:

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use TRUVADA for a condition for which it was not prescribed. Do not give TRUVADA to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about TRUVADA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about TRUVADA that is written for health professionals. For more information, you may also call 1-800-GILEAD-5 or access the TRUVADA website at www.TRUVADA.com.

Do not use TRUVADA if seal over bottle opening is broken or missing.

What are the ingredients of TRUVADA?

Active Ingredients: emtricitabine and tenofovir DF

Inactive Ingredients: Croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and pregelatinized starch (gluten free). The tablets are coated with Opadry II Blue Y-30-10701 containing FD&C Blue #2 aluminum lake, hypromellose, lactose monohydrate, titanium dioxide and triacetin.

℞ **Only**

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