

TRUVADA - emtricitabine and tenofovir disoproxil fumarate tablet, film coated
H.J. Harkins Company, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TRUVADA safely and effectively. See full prescribing information for TRUVADA.

TRUVADA® (emtricitabine/tenofovir disoproxil fumarate) tablets
Initial U.S. Approval: 2004

WARNINGS: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

See full prescribing information for complete boxed warning.

- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including VIREAD, a component of TRUVADA. (5.1)
- TRUVADA is not approved for the treatment of chronic hepatitis B virus (HBV) infection. Severe acute exacerbations of hepatitis B have been reported in patients coinfecting with HIV-1 and HBV who have discontinued TRUVADA. Hepatic function should be monitored closely in these patients. If appropriate, initiation of anti-hepatitis B therapy may be warranted. (5.2)

RECENT MAJOR CHANGES

Indications and Usage (1)	7/2011
Dosage and Administration (2.1, 2.2)	7/2011
Warnings and Precautions	
Decreases in Bone Mineral Density (5.5)	7/2011

INDICATIONS AND USAGE

TRUVADA, a combination of EMTRIVA and VIREAD, both nucleoside analog HIV-1 reverse transcriptase inhibitors, is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older. (1)

DOSAGE AND ADMINISTRATION

- Recommended dose in adults and pediatric patients (12 years of age and older and weighing greater than or equal to 35 kg): One tablet (containing 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate) once daily taken orally with or without food. (2.1)
- Dose recommended in renal impairment:
Creatinine clearance 30–49 mL/min: 1 tablet every 48 hours. (2.2)
CrCl below 30 mL/min or hemodialysis: Do not use TRUVADA. (2.2)

DOSAGE FORMS AND STRENGTHS

Tablets: 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- New onset or worsening renal impairment: Can include acute renal failure and Fanconi syndrome. Assess creatinine clearance (CrCl) before initiating treatment with TRUVADA. Monitor CrCl and serum phosphorus in patients at risk. Avoid administering Truvada with concurrent or recent use of nephrotoxic drugs. (5.3)
- Coadministration with Other Products: Do not use with drugs containing emtricitabine or tenofovir disoproxil fumarate including ATRIPLA, EMTRIVA, VIREAD; or with drugs containing lamivudine. Do not administer in combination with HEPSERA. (5.4)
- Decreases in bone mineral density (BMD): Consider assessment of BMD in patients with a history of pathologic fracture or other risk factors for osteoporosis or bone loss. (5.5)
- Redistribution/accumulation of body fat: Observed in patients receiving antiretroviral therapy. (5.6)
- Immune reconstitution syndrome: May necessitate further evaluation and treatment. (5.7)
- Triple nucleoside-only regimens: Early virologic failure has been reported in HIV-infected patients. Monitor carefully and consider treatment modification. (5.8)

----- **ADVERSE REACTIONS** -----

Most common adverse reactions (incidence greater than or equal to 10%) are diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at 1-800-GILEAD-5 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----- **DRUG INTERACTIONS** -----

- Didanosine: Tenofovir disoproxil fumarate increases didanosine concentrations. Use with caution and monitor for evidence of didanosine toxicity (e.g., pancreatitis, neuropathy) when coadministered. Consider dose reductions or discontinuations of didanosine if warranted. (7.1)
- Atazanavir: Coadministration decreases atazanavir concentrations and increases tenofovir concentrations. Use atazanavir with TRUVADA only with ritonavir; monitor for evidence of tenofovir toxicity. (7.2)
- Lopinavir/ritonavir: Coadministration increases tenofovir concentrations. Monitor for evidence of tenofovir toxicity. (7.2)

----- **USE IN SPECIFIC POPULATIONS** -----

- Pregnancy: pregnancy registry available: Enroll patients by calling 1-800-258-4263.
- Nursing mothers: Women infected with HIV should be instructed not to breast feed. (8.3)
- Pediatrics: Safety and efficacy not established in patients less than 12 years of age. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 9/2011

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FULL PRESCRIBING INFORMATION

WARNINGS: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including VIREAD, a component of TRUVADA, in combination with other antiretrovirals [See Warnings and Precautions (5.1)].

TRUVADA is not approved for the treatment of chronic hepatitis B virus (HBV) infection and the safety and efficacy of TRUVADA have not been established in patients coinfecting with HBV and HIV-1. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfecting with HBV and HIV-1 and have discontinued TRUVADA. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are coinfecting with HIV-1 and HBV and discontinue TRUVADA. If appropriate, initiation of anti-hepatitis B therapy may be warranted [See Warnings and Precautions (5.2)].

1 INDICATIONS AND USAGE

TRUVADA[®], a combination of EMTRIVA[®] and VIREAD[®], 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 and pediatric patients 12 years of age and older.

The following points should be considered when initiating therapy with TRUVADA for the treatment of HIV-1 infection:

- It is not recommended that TRUVADA be used as a component of a triple nucleoside regimen.
- TRUVADA should not be coadministered with ATRIPLA[®], EMTRIVA, VIREAD or lamivudine-containing products [See Warnings and Precautions (5.4)].
- In treatment experienced patients, the use of TRUVADA should be guided by laboratory testing and treatment history [See Clinical Pharmacology (12.4)].

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The dose of TRUVADA for adults and pediatric patients 12 years of age and older with body weight greater than or equal to 35 kg (greater than or equal to 77 lb) is one tablet (containing 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate) once daily taken orally with or without food.

2.2 Dose Adjustment for Renal Impairment

Significantly increased drug exposures occurred when EMTRIVA or VIREAD were administered to subjects 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 1. These dosing interval recommendations are based on modeling of single-dose pharmacokinetic data in non-HIV infected subjects. The safety and effectiveness of these dosing interval adjustment recommendations have not been clinically evaluated in patients with moderate renal impairment, therefore clinical response to treatment and renal function should be closely monitored in these patients [See Warnings and Precautions (5.3)].

No dose adjustment is necessary for patients with mild renal impairment (creatinine clearance 50–80 mL/min). Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients with mild renal impairment [See Warnings and Precautions (5.3)].

Table 1 Dosage Adjustment for Patients with Altered Creatinine Clearance

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

* Calculated using ideal (lean) body weight

No data are available to make dose recommendations in pediatric patients 12 years of age and older with renal impairment.

3 DOSAGE FORMS AND STRENGTHS

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.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 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 VIREAD, a component of TRUVADA, 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).

5.2 Patients Coinfected with HIV-1 and HBV

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

5.3 New Onset or Worsening Renal Impairment

Emtricitabine and tenofovir are principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of VIREAD [See Adverse Reactions (6.2)].

It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with TRUVADA. 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 HEPSERA.

Dosing interval adjustment of TRUVADA and close monitoring of renal function are recommended in all patients with creatinine clearance 30–49 mL/min, [See Dosage and Administration (2.2)]. No safety or efficacy data are available in patients with renal impairment who received TRUVADA using these dosing guidelines, so the potential benefit of TRUVADA therapy should be assessed against the potential risk of renal toxicity. TRUVADA should not be administered to patients with creatinine clearance below 30 mL/min or patients requiring hemodialysis.

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

5.4 Coadministration with Other Products

TRUVADA is a fixed-dose combination of emtricitabine and tenofovir disoproxil fumarate. TRUVADA should not be coadministered with ATRIPLA, EMTRIVA, or VIREAD. Due to similarities between emtricitabine and lamivudine, TRUVADA should not be coadministered with other drugs containing lamivudine, including Combivir (lamivudine/zidovudine), Epivir or Epivir-HBV (lamivudine), Epzicom (abacavir sulfate/lamivudine), or Trizivir (abacavir sulfate/lamivudine/zidovudine).

TRUVADA should not be administered with HEPSERA[®] (adefovir dipivoxil).

5.5 Decreases in Bone Mineral Density

Assessment of bone mineral density (BMD) should be considered for HIV-1 infected adults and pediatric patients 12 years of age and older 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.

Tenofovir Disoproxil Fumarate: In a 144-week trial of treatment-naive adult subjects, decreases in BMD were seen at the lumbar spine and hip in both arms of the trial. At Week 144, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in subjects receiving VIREAD + lamivudine + efavirenz compared with subjects receiving stavudine + lamivudine + efavirenz. Changes in BMD at the hip were similar between the two treatment groups. In both groups, the majority of the reduction in BMD occurred in the first 24–48 weeks of the trial and this reduction was sustained through 144 weeks. Twenty-eight percent of VIREAD-treated subjects vs. 21% of the comparator subjects lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 subjects in the VIREAD group and 6 subjects in the comparator group. Tenofovir disoproxil fumarate was associated with significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide, and urinary N-telopeptide), suggesting increased bone turnover. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in subjects receiving VIREAD.

In a clinical trial of HIV-1 infected pediatric subjects 12 years of age and older (Study 321), bone effects were similar to adult subjects. Under normal circumstances BMD increases rapidly in this age group. In this trial, the mean rate of bone gain was less in the VIREAD-treated group compared to the placebo group. Six VIREAD treated subjects and one placebo treated subject had significant (greater than 4%) lumbar spine BMD loss in 48 weeks. Among 28 subjects receiving 96 weeks of VIREAD, Z-scores declined by -0.341 for lumbar spine and -0.458 for total body. Skeletal growth (height) appeared to be unaffected. Markers of bone turnover in VIREAD-treated pediatric subjects 12 years of age and older suggest increased bone turnover, consistent with the effects observed in adults.

The effects of VIREAD-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. For additional information, please consult the VIREAD prescribing information.

Cases of osteomalacia (associated with proximal renal tubulopathy and which may contribute to fractures) have been reported in association with the use of VIREAD [See Adverse Reactions (6.2)].

5.6 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.

5.7 Immune Reconstitution Syndrome

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

5.8 Early Virologic Failure

Clinical trials in HIV-infected subjects have demonstrated that certain regimens that only contain three nucleoside reverse transcriptase inhibitors (NRTI) are generally less effective than triple drug regimens containing two NRTIs in combination with either a non-nucleoside reverse transcriptase inhibitor or a HIV-1 protease inhibitor. In particular, early virological failure and high rates of resistance substitutions have been reported. Triple nucleoside regimens should therefore be used with caution. Patients on a therapy utilizing a triple nucleoside-only regimen should be carefully monitored and considered for treatment modification.

6 ADVERSE REACTIONS

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

- Lactic Acidosis/Severe Hepatomegaly with Steatosis [See Boxed Warning, Warnings and Precautions (5.1)].
- Severe Acute Exacerbations of hepatitis B [See Boxed Warning, Warnings and Precautions (5.2)].
- New Onset or Worsening Renal Impairment [See Warnings and Precautions (5.3)].
- Decreases in Bone Mineral Density [See Warnings and Precautions (5.5)].
- Immune Reconstitution Syndrome [See Warnings and Precautions (5.7)].

6.1 Adverse Reactions from Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Trials in Adult Subjects

The most common adverse reactions (incidence greater than or equal to 10%, any severity) occurring in Study 934, an active-controlled clinical trial of efavirenz, emtricitabine, and tenofovir disoproxil fumarate, include diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash. See also Table 2 for the frequency of treatment-emergent adverse reactions (Grade 2–4) occurring in greater than or equal to 5% of subjects treated with efavirenz, emtricitabine, and tenofovir disoproxil fumarate in this trial.

Skin discoloration, manifested by hyperpigmentation on the palms and/or soles was generally mild and asymptomatic. The mechanism and clinical significance are unknown.

Study 934 - Treatment Emergent Adverse Reactions: In Study 934, 511 antiretroviral-naïve subjects received either VIREAD + EMTRIVA administered in combination with efavirenz (N=257) or zidovudine/lamivudine administered in combination with efavirenz (N=254). Adverse reactions observed in this trial were generally consistent with those seen in other trials in treatment-experienced or treatment-naïve subjects receiving VIREAD and/or EMTRIVA (Table 2).

**Table 2 Selected Treatment-Emergent Adverse Reactions* (Grades 2–4)
Reported in ≥5% in Any Treatment Group in Study 934 (0–144 Weeks)**

	FTC + TDF + EFV [†]	AZT/3TC + EFV
	N=257	N=254
Gastrointestinal Disorder		
Diarrhea	9%	5%
Nausea	9%	7%
Vomiting	2%	5%
General Disorders and Administration Site Condition		
Fatigue	9%	8%
Infections and Infestations		
Sinusitis	8%	4%
Upper respiratory tract infections	8%	5%
Nasopharyngitis	5%	3%
Nervous System Disorders		
Headache	6%	5%
Dizziness	8%	7%
Psychiatric Disorders		

Depression	9%	7%
Insomnia	5%	7%
Skin and Subcutaneous Tissue Disorders		
Rash event [‡]	7%	9%

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

† From Weeks 96 to 144 of the trial, subjects received TRUVADA with efavirenz in place of VIREAD + EMTRIVA with efavirenz.

‡ Rash event includes rash, exfoliative rash, rash generalized, rash macular, rash maculopapular, rash pruritic, and rash vesicular.

Laboratory Abnormalities: Laboratory abnormalities observed in this trial were generally consistent with those seen in other trials of VIREAD and/or EMTRIVA (Table 3).

Table 3 Significant Laboratory Abnormalities Reported in ≥1% of Subjects in Any Treatment Group in Study 934 (0–144 Weeks)

	FTC + TDF + EFV*	AZT/3TC + EFV
	N=257	N=254
Any ≥ Grade 3 Laboratory Abnormality	30%	26%
Fasting Cholesterol (>240 mg/dL)	22%	24%
Creatine Kinase (M: >990 U/L) (F: >845 U/L)	9%	7%
Serum Amylase (>175 U/L)	8%	4%
Alkaline Phosphatase (>550 U/L)	1%	0%
AST (M: >180 U/L) (F: >170 U/L)	3%	3%
ALT (M: >215 U/L) (F: >170 U/L)	2%	3%
Hemoglobin (<8.0 mg/dL)	0%	4%
Hyperglycemia (>250 mg/dL)	2%	1%
Hematuria (>75 RBC/HPF)	3%	2%
Glycosuria (≥3+)	<1%	1%
Neutrophils (<750/mm ³)	3%	5%
Fasting Triglycerides (>750 mg/dL)	4%	2%

* From Weeks 96 to 144 of the trial, subjects received TRUVADA with efavirenz in place of VIREAD + EMTRIVA with efavirenz.

In addition to the events described above for Study 934, other adverse reactions that occurred in at least 5% of subjects receiving EMTRIVA or VIREAD with other antiretroviral agents in clinical trials include anxiety, arthralgia, increased cough, dyspepsia, fever, myalgia, pain, abdominal pain, back pain, paresthesia, peripheral neuropathy (including peripheral neuritis and neuropathy), pneumonia, and rhinitis.

In addition to the laboratory abnormalities described above for Study 934, Grade 3/4 laboratory abnormalities of increased bilirubin ($>2.5 \times \text{ULN}$), increased pancreatic amylase ($>2.0 \times \text{ULN}$), increased or decreased serum glucose (<40 or >250 mg/dL), and increased serum lipase ($>2.0 \times \text{ULN}$) occurred in up to 3% of subjects treated with EMTRIVA or VIREAD with other antiretroviral agents in clinical trials.

Clinical Trials in Pediatric Subjects 12 Years of Age and Older

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

Tenofovir Disoproxil Fumarate: In a pediatric clinical trial conducted in subjects 12 to less than 18 years of age, the adverse reactions observed in pediatric subjects who received treatment with VIREAD were consistent with those observed in clinical trials of VIREAD in adults [*See Warnings and Precautions (5.5)*].

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of VIREAD. No additional adverse reactions have been identified during postapproval use of EMTRIVA. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders

allergic reaction, including angioedema

Metabolism and Nutrition Disorders

lactic acidosis, hypokalemia, hypophosphatemia

Respiratory, Thoracic, and Mediastinal Disorders

dyspnea

Gastrointestinal Disorders

pancreatitis, increased amylase, abdominal pain

Hepatobiliary Disorders

hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT gamma GT)

Skin and Subcutaneous Tissue Disorders

rash

Musculoskeletal and Connective Tissue Disorders

rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy

Renal and Urinary Disorders

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

General Disorders and Administration Site Conditions

asthenia

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

7 DRUG INTERACTIONS

No drug interaction trials have been conducted using TRUVADA tablets. Drug interaction trials have been conducted with emtricitabine and tenofovir disoproxil fumarate, the components of TRUVADA. This section describes clinically relevant drug interactions observed with emtricitabine and tenofovir disoproxil fumarate [See *Clinical Pharmacology (12.3)*].

7.1 Didanosine

Coadministration of TRUVADA 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.

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 *Clinical Pharmacology (12.3)*]. The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis, and neuropathy. Suppression of CD4⁺ cell counts has been observed in patients receiving tenofovir DF with didanosine 400 mg daily.

In patients weighing greater than 60 kg, 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 adult or pediatric patients weighing less than 60 kg. When coadministered, TRUVADA and Videx EC may be taken under fasted conditions or with a light meal (less than 400 kcal, 20% fat). Coadministration of didanosine buffered tablet formulation with TRUVADA should be under fasted conditions.

7.2 Atazanavir

Atazanavir has been shown to increase tenofovir concentrations [See *Clinical Pharmacology (12.3)*]. The mechanism of this interaction is unknown. Patients receiving atazanavir and TRUVADA should be monitored for TRUVADA-associated adverse reactions. TRUVADA should be discontinued in patients who develop TRUVADA-associated adverse reactions.

Tenofovir decreases the AUC and C_{min} of atazanavir [See *Clinical Pharmacology (12.3)*]. 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.

7.3 Lopinavir/Ritonavir

Lopinavir/ritonavir has been shown to increase tenofovir concentrations [See *Clinical Pharmacology (12.3)*]. The mechanism of this interaction is unknown. Patients receiving lopinavir/ritonavir and TRUVADA should be monitored for TRUVADA-associated adverse reactions. TRUVADA should be discontinued in patients who develop TRUVADA-associated adverse reactions.

7.4 Drugs Affecting Renal Function

Emtricitabine and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion [See *Clinical Pharmacology (12.3)*]. 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. Some examples include, but are not limited to acyclovir, adefovir dipivoxil, cidofovir, ganciclovir, valacyclovir, and valganciclovir. Drugs that decrease renal function may increase concentrations of emtricitabine and/or tenofovir.

8 USE IN SPECIFIC POPULATIONS

8.1 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 trials 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.

8.3 Nursing Mothers

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-1 infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV-1. 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-1 transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving TRUVADA.**

8.4 Pediatric Use

Truvada should only be administered to pediatric patients 12 years of age and older with body weight greater than or equal to 35 kg (greater than or equal to 77 lb) because it is a fixed-dose combination tablet containing a component, VIREAD, for which safety and efficacy have not been established in pediatric patients less than 12 years of age or weighing less than 35 kg (less than 77 lb) [*See Warnings and Precautions (5.5), Adverse Reactions (6.1) and Clinical Pharmacology (12.3)*].

8.5 Geriatric Use

Clinical trials 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.

8.6 Patients with Impaired Renal Function

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 below 30 mL/min and in patients with end-stage renal disease requiring dialysis [*See Dosage and Administration (2.2)*].

10 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 trials single doses of emtricitabine 1200 mg were administered to 11 subjects. 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 trial, 600 mg tenofovir disoproxil fumarate was administered to 8 subjects orally for 28 days, and no severe adverse reactions were reported. The effects of higher doses are not known.

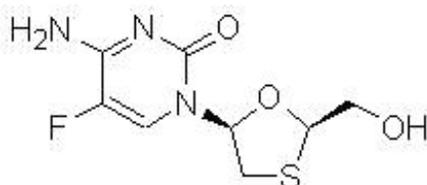
Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of VIREAD, a four-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

11 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 (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.

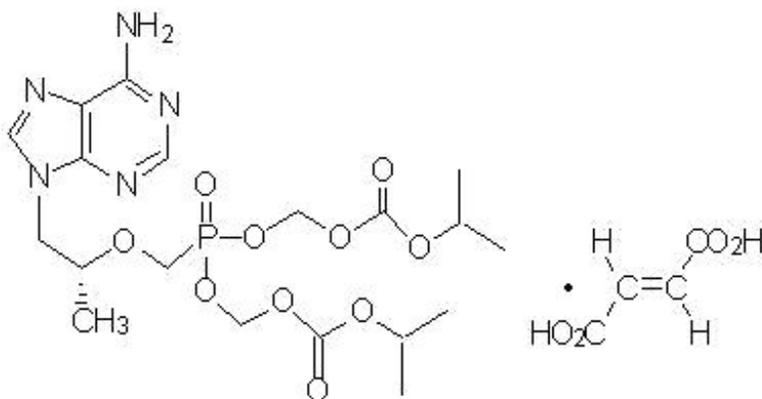
Emtricitabine: The chemical name of emtricitabine is 5-fluoro-1-(2*R*,5*S*)-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. Emtricitabine is the (-) enantiomer of a thio analog of cytidine, which differs from other cytidine analogs in that it has a fluorine in the 5-position.

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 $C_{19}H_{30}N_5O_{10}P \cdot C_4H_4O_4$ 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.

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, hydroxypropyl methylcellulose 2910, lactose monohydrate, titanium dioxide, and triacetin.

12 CLINICAL PHARMACOLOGY

For additional information on Mechanism of Action, Antiviral Activity, Resistance and Cross Resistance, please consult the EMTRIVA and VIREAD prescribing information.

12.1 Mechanism of Action

TRUVADA is a fixed-dose combination of antiviral drugs emtricitabine and tenofovir disoproxil fumarate. [See *Clinical Pharmacology* (12.4)].

12.3 Pharmacokinetics

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 4. Following oral administration of EMTRIVA, emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1–2 hours post-dose. Less than 4% of emtricitabine binds to human plasma proteins in vitro and the binding is independent of concentration over the range of 0.02–200 µg/mL. Following administration of 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 4. Following oral administration of VIREAD, maximum tenofovir serum concentrations are achieved in 1.0 ± 0.4 hour. Less than 0.7% of tenofovir binds to human plasma proteins in vitro and the binding is independent of concentration over the range of 0.01–25 µg/mL. Approximately 70–80% of the intravenous dose of tenofovir is recovered as unchanged drug in the urine. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of VIREAD, the terminal elimination half-life of tenofovir is approximately 17 hours.

Table 4 Single Dose Pharmacokinetic Parameters for Emtricitabine and Tenofovir in Adults*

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

- * NC = Not calculated
- † Median (range)
- ‡ Mean (\pm SD)
- § 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 trials, 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 subjects.

Pediatric Patients

TRUVADA should not be administered to pediatric patients less than 12 years of age or weighing less than 35 kg (less than 77 lb).

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

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

Geriatric Patients

Pharmacokinetics of emtricitabine and tenofovir have not been fully evaluated in the elderly (65 years of age and older).

Patients with Impaired Renal Function

The pharmacokinetics of emtricitabine and tenofovir are altered in subjects with renal impairment [See *Warnings and Precautions (5.3)*]. In adult subjects with creatinine clearance below 50 mL/min, C_{\max} , and $\text{AUC}_{0-\infty}$ 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 below 30 mL/min and in patients with end-stage renal disease requiring dialysis [See Dosage and Administration (2.2)].

Patients with Hepatic Impairment

The pharmacokinetics of tenofovir following a 300 mg dose of VIREAD have been studied in non-HIV infected subjects with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in subjects with hepatic impairment compared with unimpaired subjects. The pharmacokinetics of TRUVADA or 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.

Assessment of Drug Interactions

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

No clinically significant drug interactions have been observed between emtricitabine and famciclovir, indinavir, stavudine, tenofovir disoproxil fumarate, and zidovudine (see Tables 5 and 6). Similarly, no clinically significant drug interactions have been observed between tenofovir disoproxil fumarate and abacavir, efavirenz, emtricitabine, entecavir, indinavir, lamivudine, lopinavir/ritonavir, methadone, nelfinavir, oral contraceptives, ribavirin, saquinavir/ritonavir, and tacrolimus in trials conducted in healthy volunteers (see Tables 7 and 8).

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

Coadministered Drug	Dose of Coadministered Drug (mg)	Emtricitabine Dose (mg)	N	% Change of Emtricitabine Pharmacokinetic Parameters [†] (90% CI)		
				C _{max}	AUC	C _{min}
Tenofovir DF	300 once daily × 7 days	200 once daily × 7 days	17			↑ 20 (↑ 12 to ↑ 29)
Zidovudine	300 twice daily × 7 days	200 once daily × 7 days	27			
Indinavir	800 × 1	200 × 1	12			NA
Famciclovir	500 × 1	200 × 1	12			NA
Stavudine	40 × 1	200 × 1	6			NA

* All interaction trials conducted in healthy volunteers.

[†] ↑ = Increase; ↓ = Decrease; = No Effect; NA = Not Applicable

Table 6 Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Emtricitabine*

Coadministered Drug	Dose of Coadministered Drug (mg)	Emtricitabine Dose (mg)	N	% Change of Coadministered Drug Pharmacokinetic Parameters [†] (90% CI)		
				C _{max}	AUC	C _{min}
Tenofovir DF	300 once daily × 7 days	200 once daily × 7 days	17			
Zidovudine	300 twice daily	200 once daily	27	↑ 17	↑ 13	

Zidovudine	× 7 days	× 7 days	≤/	(↑ 0 to ↑ 38)	(↑ 5 to ↑ 20)	
Indinavir	800 × 1	200 × 1	12			NA
Famciclovir	500 × 1	200 × 1	12			NA
Stavudine	40 × 1	200 × 1	6			NA

* All interaction trials conducted in healthy volunteers.

† ↑ = Increase; ↓ = Decrease; = No Effect; NA = Not Applicable

Table 7 Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir* in the Presence of the Coadministered Drug

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Tenofovir Pharmacokinetic Parameters† (90% CI)		
			C _{max}	AUC	C _{min}
Abacavir	300 once	8			NC
Atazanavir‡	400 once daily × 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 × 7 days	14			
Efavirenz	600 once daily × 14 days	29			
Emtricitabine	200 once daily × 7 days	17			
Entecavir	1 mg once daily × 10 days	28			
Indinavir	800 three times daily × 7 days	13	↑ 14 (↓ 3 to ↑ 33)		
Lamivudine	150 twice daily × 7 days	15			
Lopinavir/Ritonavir	400/100 twice daily × 14 days	24		↑ 32 (↑ 25 to ↑ 38)	↑ 51 (↑ 37 to ↑ 66)
Nelfinavir	1250 twice daily × 14 days	29			
Saquinavir/Ritonavir	1000/100 twice daily × 14 days	35			↑ 23 (↑ 16 to ↑ 30)
Tacrolimus	0.05 mg/kg twice daily × 7 days	21	↑ 13 (↑ 1 to ↑ 27)		

* Subjects received VIREAD 300 mg once daily.

† Increase = ↑; Decrease = ↓; No Effect = ; NC = Not Calculated

‡ Reyataz Prescribing Information

Table 8 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* (90% CI)		
			C _{max}	AUC	C _{min}
			↑ 13		

Abacavir	300 once	8	↑ 12 (↓ 1 to ↑ 26)		NA
Atazanavir [†]	400 once daily × 14 days	34	↓ 21 (↓ 27 to ↓ 14)	↓ 25 (↓ 30 to ↓ 19)	↓ 40 (↓ 48 to ↓ 32)
Atazanavir [†]	Atazanavir/Ritonavir 300/100 once daily × 42 days	10	↓ 28 (↓ 50 to ↑ 5)	↓ 25 [‡] (↓ 42 to ↓ 3)	↓ 23 [‡] (↓ 46 to ↑ 10)
Efavirenz	600 once daily × 14 days	30			
Emtricitabine	200 once daily × 7 days	17			↑ 20 (↑ 12 to ↑ 29)
Indinavir	800 three times daily × 7 days	12	↓ 11 (↓ 30 to ↑ 12)		
Entecavir	1 mg once daily × 10 days	28		↑ 13 (↑ 11 to ↑ 15)	
Lamivudine	150 twice daily × 7 days	15	↓ 24 (↓ 34 to ↓ 12)		
Lopinavir Ritonavir	Lopinavir/Ritonavir 400/100 twice daily × 14 days	24			
Methadone [§]	40–110 once daily × 14 days [¶]	13			
Nelfinavir M8 metabolite	1250 twice daily × 14 days	29			
Oral Contraceptives [#]	Ethinyl Estradiol/ Norgestimate (Ortho- Tricyclen) Once daily × 7 days	20			
Ribavirin	600 once	22			NA
Saquinavir Ritonavir	Saquinavir/Ritonavir 1000/100 twice daily × 14 days	32	↑ 22 (↑ 6 to ↑ 41)	↑ 29 ^D (↑ 12 to ↑ 48)	↑ 47 ^D (↑ 23 to ↑ 76) ↑ 23 (↑ 3 to ↑ 46)
Tacrolimus	0.05 mg/kg twice daily × 7 days	21			

* Increase = ↑; Decrease = ↓; No Effect = ; NA = Not Applicable

[†] Reyataz Prescribing Information

[‡] In HIV-infected subjects, 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.

[§] R-(active), S- and total methadone exposures were equivalent when dosed alone or with VIREAD.

[¶] Individual subjects were maintained on their stable methadone dose. No pharmacodynamic alterations (opiate toxicity or withdrawal signs or symptoms) were reported.

[#] Ethinyl estradiol and 17-deacetyl norgestimate (pharmacologically active metabolite) exposures were equivalent when dosed alone or with VIREAD.

^D Increases in AUC and C_{min} are not expected to be clinically relevant; hence no dose adjustments are required when tenofovir DF and ritonavir-boosted saquinavir are coadministered.

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 trials, 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 9 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. See *Drug Interactions (7.1)* regarding use of didanosine with VIREAD.

Table 9 Drug Interactions: Pharmacokinetic Parameters for Didanosine in the Presence of VIREAD

Didanosine* Dose (mg)/Method of Administration*	VIREAD Method of Administration*	N	% Difference (90% CI) vs. Didanosine 400 mg Alone, Fasted†	
			C_{max}	AUC
Buffered tablets				
400 once daily‡ × 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 hours 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 hours 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)

* Administration with food was with a light meal (~373 kcal, 20% fat).

† Increase = ↑; Decrease = ↓; No Effect =

‡ Includes 4 subjects weighing <60 kg receiving ddI 250 mg.

12.4 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 cell culture antiviral activity of emtricitabine and tenofovir together, synergistic antiviral effects were observed.

Emtricitabine: The antiviral activity of emtricitabine against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. The 50% effective concentration (EC₅₀) 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. Emtricitabine displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC₅₀ values ranged from 0.007–0.075 μM) and showed strain specific activity against HIV-2 (EC₅₀ values ranged from 0.007–1.5 μM).

Tenofovir Disoproxil Fumarate: The 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 EC₅₀ 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 cell culture against HIV-1 clades A, B, C, D, E, F, G and O (EC₅₀ values ranged from 0.5–2.2 μM) and showed strain specific activity against HIV-2 (EC₅₀ values ranged from 1.6 μM to 5.5 μM).

Resistance

Emtricitabine and Tenofovir Disoproxil Fumarate: HIV-1 isolates with reduced susceptibility to the combination of emtricitabine and tenofovir have been selected in cell culture. Genotypic analysis of these isolates identified the M184V/I and/or K65R amino acid substitutions in the viral RT.

In a clinical trial of treatment-naïve subjects [*Study 934, see Clinical Studies (14.1)*], resistance analysis was performed on HIV-1 isolates from all confirmed virologic failure subjects with greater than 400 copies/mL of HIV-1 RNA at Week 144 or early discontinuation. Development of efavirenz resistance-associated substitutions occurred most frequently and was similar between the treatment arms. The M184V amino acid substitution, associated with resistance to EMTRIVA and lamivudine, was observed in 2/19 analyzed subjects isolates in the EMTRIVA + VIREAD group and in 10/29 analyzed subjects isolates in the zidovudine/lamivudine group. Through 144 weeks of Study 934, no subjects have developed a detectable K65R substitution in their HIV-1 as analyzed through standard genotypic analysis.

Emtricitabine: Emtricitabine-resistant isolates of HIV-1 have been selected in cell culture and in vivo. Genotypic analysis of these isolates showed that the reduced susceptibility to emtricitabine was associated with a substitution in the HIV-1 RT gene at codon 184 which resulted in an amino acid substitution of methionine by valine or isoleucine (M184V/I).

Tenofovir Disoproxil Fumarate: HIV-1 isolates with reduced susceptibility to tenofovir have been selected in cell culture. These viruses expressed a K65R substitution in RT and showed a 2–4 fold reduction in susceptibility to tenofovir.

In treatment-naïve subjects, isolates from 8/47 (17%) analyzed subjects developed the K65R substitution in the VIREAD arm through 144 weeks; 7 occurred in the first 48 weeks of treatment and 1 at Week 96. In treatment-experienced subjects, 14/304 (5%) isolates from subjects failing VIREAD through Week 96 showed greater than 1.4 fold (median 2.7) reduced susceptibility to tenofovir. Genotypic analysis of the resistant isolates showed a substitution 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 cell culture 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 cell culture to didanosine, stavudine, tenofovir, zidovudine, and NNRTIs (delavirdine, efavirenz, and nevirapine). 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 substitutions 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 subjects (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. Subjects whose virus expressed an L74V substitution without zidovudine resistance associated substitutions (N=8) had reduced response to VIREAD. Limited data are available for patients whose virus expressed a Y115F substitution (N=3), Q151M substitution (N=2), or T69 insertion (N=4), all of whom had a reduced response.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Emtricitabine: In long-term oral 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/kg/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 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-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 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.

13.2 Animal Toxicology and/or Pharmacology

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.

14 CLINICAL STUDIES

Clinical Study 934 supports the use of TRUVADA tablets for the treatment of HIV-1 infection. Additional data in support of the use of TRUVADA are derived from Study 903, in which lamivudine and tenofovir disoproxil fumarate (tenofovir DF) were used in combination in treatment-naïve adults, and clinical Study 303 in which emtricitabine and lamivudine demonstrated comparable efficacy, safety and resistance patterns as part of multidrug regimens. For additional information about these trials, please consult the prescribing information for tenofovir DF and emtricitabine.

14.1 Study 934

Data through 144 weeks are reported for Study 934, a randomized, open-label, active-controlled multicenter trial comparing emtricitabine + tenofovir DF administered in combination with efavirenz versus zidovudine/lamivudine fixed-dose combination administered in combination with efavirenz in 511 antiretroviral-naïve subjects. From Weeks 96 to 144 of the trial, subjects received TRUVADA with efavirenz in place of emtricitabine + tenofovir DF with efavirenz. Subjects had a mean age of 38 years (range 18–80), 86% were male, 59% were Caucasian and 23% were Black. The mean baseline CD4⁺ cell count was 245 cells/mm³ (range 2–1191) and median baseline plasma HIV-1 RNA was 5.01 log₁₀ copies/mL (range 3.56–6.54). Subjects were stratified by baseline CD4⁺ cell count (< or ≥200 cells/mm³); 41% had CD4⁺ cell counts <200 cells/mm³ and 51% of subjects had baseline viral loads >100,000 copies/mL. Treatment outcomes through 48 and 144 weeks for those subjects who did not have efavirenz resistance at baseline are presented in Table 10.

Table 10 Outcomes of Randomized Treatment at Week 48 and 144 (Study 934)

Outcomes	At Week 48		At Week 144	
	FTC + TDF + EFV (N=244)	AZT/3TC + EFV (N=243)	FTC + TDF + EFV (N=227)*	AZT/3TC + EFV (N=229)*
Responder [†]	84%	73%	71%	58%
Virologic failure [‡]	2%	4%	3%	6%
Rebound	1%	3%	2%	5%
Never suppressed	0%	0%	0%	0%
Change in antiretroviral regimen	1%	1%	1%	1%
Death	<1%	1%	1%	1%
Discontinued due to adverse event	4%	9%	5%	12%

Discontinued for other reasons [§]	10%	14%	20%	22%
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* Subjects who were responders at Week 48 or Week 96 (HIV-1 RNA <400 copies/mL) but did not consent to continue trial after Week 48 or Week 96 were excluded from analysis.

† Subjects achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Weeks 48 and 144.

‡ Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Weeks 48 and 144.

§ Includes lost to follow-up, subject withdrawal, noncompliance, protocol violation and other reasons.

Through Week 48, 84% and 73% of subjects in the emtricitabine + tenofovir DF group and the zidovudine/lamivudine group, respectively, achieved and maintained HIV-1 RNA <400 copies/mL (71% and 58% through Week 144). The difference in the proportion of subjects who achieved and maintained HIV-1 RNA <400 copies/mL through 48 weeks largely results from the higher number of discontinuations due to adverse events and other reasons in the zidovudine/lamivudine group in this open-label trial. In addition, 80% and 70% of subjects in the emtricitabine + tenofovir DF group and the zidovudine/lamivudine group, respectively, achieved and maintained HIV-1 RNA <50 copies/mL through Week 48 (64% and 56% through Week 144). The mean increase from baseline in CD4⁺ cell count was 190 cells/mm³ in the emtricitabine + tenofovir DF group and 158 cells/mm³ in the zidovudine/lamivudine group at Week 48 (312 and 271 cells/mm³ at Week 144).

Through 48 weeks, 7 subjects in the emtricitabine + tenofovir DF group and 5 subjects in the zidovudine/lamivudine group experienced a new CDC Class C event (10 and 6 subjects through 144 weeks).

16 HOW SUPPLIED/STORAGE AND HANDLING

The blue, capsule-shaped, film-coated, tablets contain 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate (which is equivalent to 245 mg of tenofovir disoproxil), are debossed with "GILEAD" on one side and with "701" on the other side, and are available in unit of use bottles (containing a desiccant [silica gel canister or sachet] and closed with a child-resistant closure) of:

- 30 tablets (NDC 61958-0701-1)

Store at 25 °C (77 °F), excursions permitted to 15–30 °C (59–86 °F) (see USP Controlled Room Temperature).

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

17 PATIENT COUNSELING INFORMATION and FDA-APPROVED PATIENT LABELING

Information for Patients

Patients should be advised that:

- TRUVADA is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician when using TRUVADA.
- The use of TRUVADA has not been shown to reduce the risk of transmission of HIV-1 to others through sexual contact or blood contamination. Patients should be advised to continue to practice safer sex and to use latex or polyurethane condoms to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions or blood. Patients should be advised never to re-use or share needles.
- 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.

- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Treatment with TRUVADA should be suspended in any patients who develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity (including nausea, vomiting, unusual or unexpected stomach discomfort, and weakness) [See Warnings and Precautions (5.1)].
- All patients with HIV-1 should be tested for hepatitis B virus (HBV) before initiating antiretroviral therapy.
- Severe acute exacerbations of hepatitis B have been reported in patients who are coinfecting with HBV and HIV-1 and have discontinued TRUVADA.
- Renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported in association with the use of VIREAD. TRUVADA should be avoided with concurrent or recent use of a nephrotoxic agent [See Warnings and Precautions (5.3)]. Dosing interval of TRUVADA may need adjustment in patients with renal impairment [See Dosage and Administration (2.2)].
- TRUVADA should not be coadministered with ATRIPLA, EMTRIVA, or VIREAD; or with drugs containing lamivudine, including Combivir (lamivudine/zidovudine), Epivir or Epivir-HBV (lamivudine), Epzicom (abacavir sulfate/lamivudine), or Trizivir (abacavir sulfate/lamivudine/zidovudine) [See Warnings and Precautions (5.4)].
- TRUVADA should not be administered with HEPSERA [See Warnings and Precautions (5.4)].
- Decreases in bone mineral density have been observed with the use of VIREAD. Bone monitoring should be considered in patients who have a history of pathologic bone fracture or at risk for osteopenia [See Warnings and Precautions (5.5)].

FDA-Approved Patient Labeling

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.
- **If you are also infected with the hepatitis B virus (HBV)**, you 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-1 (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-1 medicines to treat people with HIV-1 infection. TRUVADA is for adults and pediatric patients 12 years of age and older. TRUVADA has not been studied in children under age 12 or weighing less than 35 kg (77 lb) or in 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-1 reverse transcriptase, a chemical in your body (enzyme) that is needed for HIV-1 to multiply. TRUVADA lowers the amount of HIV-1 in the blood (viral load). TRUVADA may also help to increase the number of T cells (CD4⁺ cells). Lowering the amount of HIV-1 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-1 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-1 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-1 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.
- Do not take TRUVADA if you are already taking ATRIPLA[®], Combivir (lamivudine/zidovudine), EMTRIVA, Epivir or Epivir-HBV (lamivudine), Epzicom (abacavir sulfate/lamivudine), Trizivir (abacavir sulfate/lamivudine/zidovudine), or VIREAD because these medicines contain the same or similar active ingredients.
- Do not take TRUVADA to treat your HIV infection if you are also taking HEPSERA[®] to treat your HBV infection.

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:

- Videx, Videx EC (didanosine). 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.** Also, the dose of didanosine may need to be reduced.
- 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. TRUVADA may decrease the amount of Reyataz in your blood. If you are taking TRUVADA and Reyataz together, you should also be taking Norvir (ritonavir).

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-1 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-1 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.
 - ATRIPLA, Combivir (lamivudine/zidovudine), EMTRIVA, Epivir or Epivir-HBV (lamivudine), Epzicom (abacavir sulfate/lamivudine), Trizivir (abacavir sulfate/lamivudine/zidovudine), or VIREAD.
- TRUVADA should not be used with these medicines.**
- TRUVADA should not be used with HEPSERA.

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-1 and HBV infection. TRUVADA is not approved for the treatment of hepatitis B virus infection. If you have advanced liver disease and stop treatment with TRUVADA, the "flare-up" of hepatitis B may cause your liver function to decline.
- **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).** Laboratory tests show changes in the bones of patients treated with VIREAD, a component of TRUVADA. Some HIV patients treated with VIREAD developed thinning of the bones (osteopenia) which could lead to fractures. 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. Additionally, bone pain and softening of the bone (which may contribute to fractures) may occur as a consequence of kidney problems.

Other side effects with TRUVADA when used with other anti-HIV-1 medicines include:

- Changes in body fat have been seen in some patients taking TRUVADA and other anti-HIV-1 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.
- In some patients with advanced HIV infection (AIDS), signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor immediately.

The most common side effects of EMTRIVA or VIREAD when used with other anti-HIV-1 medicines are: diarrhea, dizziness, nausea, headache, fatigue, abnormal dreams, sleeping problems, rash, depression, and vomiting. Additional side effects are lactic acidosis, kidney problems (including decline or failure of kidney function), inflammation of the pancreas, inflammation of the liver, allergic reaction (including swelling of the face, lips, tongue, or throat), shortness of breath, pain, fatty liver, stomach pain, weakness, indigestion, intestinal gas, and high volume of urine and thirst caused by kidney problems. Muscle pain and muscle weakness, bone pain, and softening of the bone (which may contribute to fractures) as a consequence of kidney problems have been reported. Skin discoloration (small spots or freckles) may also happen with TRUVADA.

These are not all the side effects of TRUVADA. 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 disoproxil fumarate

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, hydroxypropyl methylcellulose 2910, lactose monohydrate, titanium dioxide, and triacetin.

R_x Only

July 2011

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21-752-GS-024

PRINCIPAL DISPLAY PANEL - Representative Bottle Label

NDC 61958-0701-1

Truvada[®]
(emtricitabine and tenofovir
disoproxil fumarate)

Tablets

30 tablets

R_x only

Repacked by:

H.J. Harkins Company, Inc.

Nipomo, CA 93444

52959-969-03 RX Only: #XXXXXXXX #XXX CAUTION: Federal law PROHIBITS the transfer of this drug to anyone other than the person to whom prescribed and prohibits dispensing without a prescription unless OTC. See outsert for add'l RX info KEEP OUT O REACH OF CHILDREN. Store in a cool dry place 68 to 77 degrees F.

TRUVADA TABLET

Lot #: TVA01ZD
Mfg: GILEAD
Exp: 06/11 Compare to: Truvada Tablet
Mfg Canada Mfg. NDC: 61958-0701-1
Loc.: Pill ID: Blue film-coated tablets

Take as directed by your Doctor or
See outsert for usual dosage information

TRUVADA TABLET		
52959-969-03	Qty #3	
06/11	Lot TVA01ZD	
Truvada Tablet	61958-0701-1	

TRUVADA TABLET		
52959-969-03	Qty #3	
06/11	Lot TVA01ZD	
Truvada Tablet	61958-0701-1	

TRUVADA TABLET		
52959-969-03	Qty #3	
06/11	Lot TVA01ZD	
Truvada Tablet	61958-0701-1	

TRUVADA TABLET		
52959-969-03	Qty #3	
06/11	Lot TVA01ZD	
Truvada Tablet	61958-0701-1	

Repack: HJ Harkins Co., Inc. Nipomo., CA 93444
Dispense in tight, child & light-resistant container per USP

TRUVADA

emtricitabine and tenofovir disoproxil fumarate tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:52959-969(NDC:61958-0701)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
emtricitabine (UNII: G70B4ETF4S) (emtricitabine - UNII:G70B4ETF4S)	emtricitabine	200 mg
tenofovir disoproxil fumarate (UNII: OTT9J7900I) (tenofovir - UNII:99YXE507IL)	tenofovir disoproxil fumarate	300 mg

Inactive Ingredients

Ingredient Name	Strength
croscarmellose sodium (UNII: M28OL1HH48)	
lactose monohydrate (UNII: EWQ57Q8I5X)	
magnesium stearate (UNII: 70097M6I30)	
cellulose, microcrystalline (UNII: OP1R32D61U)	
starch, corn (UNII: O8232NY3SJ)	

water (UNII: 059QF0K00R)	
FD&C Blue No. 2 (UNII: L06K8R7DQK)	
aluminum oxide (UNII: LM26O6933)	
hypromelloses (UNII: 3NXW29V3WO)	
titanium dioxide (UNII: 15FIX9V2JP)	
triacetin (UNII: XHX3C3X673)	

Product Characteristics			
Color	BLUE	Score	no score
Shape	OVAL (Capsule-shaped)	Size	19mm
Flavor		Imprint Code	GILEAD;70 1
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:52959-969-03	30 in 1 BOTTLE, PLASTIC		

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021752	08/02/2004	

Labeler - H.J. Harkins Company, Inc. (147681894)

Establishment			
Name	Address	ID/FEI	Business Operations
Gilead Sciences, Inc.		185049848	manufacture