

Product Monograph

PrTruvada[®]

(Emtricitabine/Tenofovir Disoproxil Fumarate Tablets)

(200 mg/300 mg)

Antiretroviral Agent

Gilead Sciences, Inc.
Foster City, CA 94404
USA

Date of Revision: May 25, 2009

Gilead Sciences Canada, Inc.
Mississauga L5N 2W3
Canada

www.gilead.com

Submission Control No.: 128424

TABLE OF CONTENTS

PART I. HEALTH PROFESSIONAL INFORMATION	3
SUMMARY PRODUCT INFORMATION	3
INDICATIONS AND CLINICAL USE	3
CONTRAINDICATIONS	3
WARNINGS AND PRECAUTIONS.....	4
ADVERSE REACTIONS.....	9
DRUG INTERACTIONS.....	14
DOSAGE AND ADMINISTRATION	20
OVERDOSAGE	21
ACTION AND CLINICAL PHARMACOLOGY	22
STORAGE AND STABILITY.....	26
SPECIAL HANDLING INSTRUCTIONS	26
DOSAGE FORMS, COMPOSITION AND PACKAGING	26
PART II. SCIENTIFIC INFORMATION	27
PHARMACEUTICAL INFORMATION.....	27
CLINICAL TRIALS.....	28
DETAILED PHARMACOLOGY	36
VIROLOGY (MICROBIOLOGY).....	36
TOXICOLOGY	39
REFERENCES	41
PART III. CONSUMER INFORMATION	42

PART I. HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet Emtricitabine 200 mg/ Tenofovir Disoproxil Fumarate 300 mg	lactose monohydrate, pregelatinized starch (gluten free).

For a complete listing, see Dosage Forms, Composition and Packaging section.

TRUVADA Tablets are a fixed-dose combination containing emtricitabine (also known as EMTRIVA[®]) and tenofovir disoproxil fumarate (also known as VIREAD[®]).

INDICATIONS AND CLINICAL USE

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.

Additional important information regarding the use of 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 administered with EMTRIVA, VIREAD, ATRIPLA[®] or lamivudine-containing products (see WARNINGS AND PRECAUTIONS).
- In treatment-experienced patients, the use of TRUVADA should be guided by laboratory testing and treatment history (see VIROLOGY).

Geriatrics (>65 years of age)

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.

Pediatrics (<18 years of age)

Safety and effectiveness in pediatric patients have not been established.

CONTRAINDICATIONS

TRUVADA is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the product. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Lactic Acidosis and 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, alone or in combination with other antiretrovirals (see **WARNINGS and PRECAUTIONS**).

- **Post-Treatment Exacerbation of Hepatitis**

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 co-infected with HBV and HIV. Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with HBV and HIV 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 co-infected with HIV and HBV and discontinue TRUVADA. If appropriate, initiation of anti-hepatitis B therapy may be warranted (see **WARNINGS and PRECAUTIONS**).

- **Nephrotoxicity**

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 during clinical practice (see **WARNINGS and PRECAUTIONS**).

General

TRUVADA is a fixed-dose combination of emtricitabine and tenofovir disoproxil fumarate. TRUVADA should not be co-administered with EMTRIVA, VIREAD or ATRIPLA. Due to similarities between emtricitabine and lamivudine, TRUVADA should not be co-administered with other drugs containing lamivudine such as COMBIVIR[®], 3TC[®], HEPTOVIR[®], KIVEXA[®] or TRIZIVIR[®].

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

Clinical studies in HIV-infected patients 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 mutations 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.

Bone Effects

In Study 903 through 144 weeks, decreases from baseline in bone mineral density (BMD) were seen at the lumbar spine and hip in both VIREAD and stavudine treatment arms of the study and significantly greater decreases were seen in the lumbar spine measurement in the

VIREAD group relative to the stavudine group. Clinically relevant fractures were reported in both treatment groups. Increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide, and urinary N-telopeptide) were observed, suggesting increased bone turnover. 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.

Cases of osteomalacia (associated with proximal renal tubulopathy and infrequently contributing to fractures) have been reported in association with the use of VIREAD (see **ADVERSE REACTIONS, Post Market Adverse Drug Reactions**).

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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Emtricitabine: In long-term oral carcinogenicity studies of emtricitabine, no drug-related increase in tumor incidence was 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: Tenofovir DF did not show any carcinogenic potential in a long-term oral carcinogenicity study in rats. A long-term oral carcinogenicity study in mice showed a low incidence of duodenal tumors, considered likely related to high local concentrations in the gastrointestinal tract at the high dose of 600 mg/kg/day. The mechanism of tumor formation in mice and potential relevance for humans are uncertain.

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 at doses up to 2000 mg/kg when administered orally to male mice.

There were no effects on fertility, mating performance or early embryonic development when tenofovir disoproxil fumarate was administered at 600 mg/kg/day to male rats 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. A dose of 600 mg/kg/day is equivalent to 19 times the human dose based on body surface area comparisons.

Endocrine and Metabolism

Fat Redistribution

Redistribution/accumulation of body fat (lipodystrophy) 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.

Hepatic/Biliary/Pancreatic

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogs, including tenofovir disoproxil fumarate, a component of TRUVADA, alone or in combination with other antiretrovirals in the treatment of HIV infection. 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).

Hepatic Impairment

Tenofovir and tenofovir disoproxil are not metabolized by liver enzymes. Clinically relevant pharmacokinetic changes in patients with hepatic impairment are not observed. Therefore, no dose adjustment is required in patients with hepatic impairment. Emtricitabine has not been evaluated in patients with hepatic impairment; however, emtricitabine has not been shown to be metabolized by liver enzymes, so the impact of liver impairment is likely to be limited. The safety and efficacy of TRUVADA has not been established or specifically studied in patients with underlying liver disorders. Patients with chronic hepatitis B or C and treated with antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

Pancreatitis

Pancreatitis has occurred during therapy with combination regimens that included tenofovir disoproxil fumarate (VIREAD). Caution should be used when administering nucleoside analogues (including TRUVADA) to patients with a history of pancreatitis or risk factors for

the development of pancreatitis. Therapy should be suspended in patients with suspected pancreatitis.

Immune

Immune Reconstitution

During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as MAC, CMV, PCP and TB), which may necessitate further evaluation and treatment.

Renal

Nephrotoxicity

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 in association with the use of VIREAD in clinical practice (see **ADVERSE REACTIONS, Post Market Adverse Drug Reactions and DRUG INTERACTIONS**). 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.

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.

Particular caution should be exercised when administering TRUVADA to patients with known risk factors for renal disease and a history of renal dysfunction; however, cases of renal failure have also been reported in patients with no known risk factors. TRUVADA should be avoided with concurrent or recent use of a nephrotoxic agent.

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**). No safety and efficacy data are available in patients with renal dysfunction who received TRUVADA using these guidelines, and so the potential benefit of TRUVADA should be assessed against the potential risk of renal toxicity. TRUVADA should not be administered to patients with creatinine clearance <30 mL/min or patients requiring hemodialysis.

Special Populations

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 approved for the treatment of chronic HBV infection and the safety and efficacy of TRUVADA have not been

established in patients co-infected with HBV and HIV. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfecting with HBV and HIV after the discontinuation of TRUVADA. In some patients infected with HBV and treated with EMTRIVA, the exacerbations of hepatitis B were associated with liver decompensation and liver failure. Hepatic function should be closely monitored with both clinical and laboratory follow up for at least several months in patients who are co-infected with HIV and HBV and discontinue TRUVADA. If appropriate, initiation of anti-hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, post-treatment exacerbation of hepatitis may lead to hepatic decompensation. Therefore, in these patients, discontinuation of treatment without initiation of alternative anti-hepatitis B therapy is not recommended.

Pregnant Women

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, TRUVADA should be used in pregnant women only if the potential benefits outweigh the potential risks to the fetus.

Emtricitabine: The incidence of fetal variations and malformations was not increased in embryo-fetal 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. Reduced pup body weights, survival and delay in sexual maturation was observed in a peri- and postnatal toxicity study in rats at the maternally toxic doses of 450 and 600 mg/kg (approximately 14 and 19 times the human dose based on body surface area comparisons).

Antiretroviral Pregnancy Registry

To monitor fetal outcomes of pregnant women exposed to ART (antiretroviral therapy) including TRUVADA, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients by calling 800-258-4263.

Nursing Women

HIV-infected mothers should not breast-feed their infants to avoid risking postnatal transmission of HIV. Studies in rats and rhesus monkeys have demonstrated that tenofovir is secreted in milk. It is not known whether emtricitabine or tenofovir 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.**

Pediatrics (<18 years of age)

Safety and effectiveness in pediatric patients have not been established.

Geriatrics (>65 years of age)

Clinical studies of EMTRIVA or VIREAD did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. In general, dose selection for the elderly patient 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 Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

TRUVADA: Four hundred and forty-seven HIV-1 infected patients have received combination therapy with EMTRIVA or VIREAD with either a non-nucleoside reverse transcriptase inhibitor or protease inhibitor for 48 weeks in ongoing clinical studies.

Study 934 - Treatment Emergent Adverse Events: Assessment of adverse reactions is based on data from Study 934 in which 511 antiretroviral-naïve patients received either EMTRIVA + VIREAD administered in combination with efavirenz (N=257) or Combivir[®] (lamivudine/zidovudine) administered in combination with efavirenz (N=254). Adverse events observed in this study were generally consistent with those seen in other studies in treatment experienced or treatment-naïve patients (Table 1).

Table 1. Selected Treatment-Emergent Adverse Events (Grades 2–4) Reported in ≥3% in Any Treatment Group in Study 934 (0–48 Weeks)

	EMTRIVA+VIREAD+EFV	AZT/3TC+EFV
	N=257	N=254
Blood and Lymphatic System Disorders		
Anemia	<1%	5%
Gastrointestinal Disorder		
Diarrhea	7%	4%
Nausea	8%	6%
Vomiting	1%	4%
General Disorders and Administration Site Condition		
Fatigue	7%	6%
Infections and Infestations		
Sinusitis	4%	2%
Upper respiratory tract infections	3%	3%
Nasopharyngitis	3%	1%
Nervous System Disorders		
Somnolence	3%	2%
Headache	5%	4%
Dizziness	8%	7%
Psychiatric Disorders		
Depression	4%	7%
Insomnia	4%	5%
Abnormal dreams	4%	3%
Skin and Subcutaneous Tissue Disorders		
Rash	5%	4%

Patients who received treatment up to 144 weeks in Study 934 reported adverse events similar in nature and severity to those reported in the first 48 weeks.

Through 48 weeks, 7 patients in the EMTRIVA + VIREAD group and 5 patients in the lamivudine/zidovudine group experienced a new CDC Class C event (10 and 6 patients, respectively, through 144 weeks). Renal safety assessed by laboratory abnormalities was similar in the two groups and no patient discontinued study drug due to renal events. At

Weeks 48 and 144, total limb fat (as measured by dual-energy x-ray absorptiometry) was significantly less in a subgroup of patients in the lamivudine/zidovudine group compared to the tenofovir/emtricitabine subgroup (see Table 2).

Table 2. Study 934 Total Limb Fat at Week 48 and 144 (Dual-Energy X-Ray Absorptiometry)

	EMTRIVA + VIREAD + EFV	AZT/3TC +EFV
Week 48¹	N=51	N=49
Total Limb Fat (kg) (Mean ± S.D.)	8.9 ±5.4	6.9 ±3.9
Week 144²	N=145	N=124
Total Limb Fat (kg) (Mean ± S.D.)	9.2 ±5.4	6.5 ±4.3

¹P=0.03 for the comparison between arms

²P<0.001 for the comparison between arms

Laboratory Abnormalities: Laboratory Abnormalities observed in this study were generally consistent with those seen in other studies (Table 3).

Table 3. Grade 3/4 Laboratory Abnormalities Reported in ≥1% in Any Treatment Group in Study 934 (0–48 Weeks)

	EMTRIVA+VIREAD+EFV N=257	AZT/3TC+EFV N=254
Any ≥ Grade 3 Laboratory Abnormality	25%	22%
Fasting Cholesterol (>240 mg/dL)	15%	17%
Creatine Kinase (M: >990 U/L) (F: >845 U/L)	7%	6%
Serum Amylase (>175U/L)	7%	3%
Alkaline Phosphatase (>550 U/L)	1%	0%
AST (M: >180 U/L) (F: >170 U/L)	3%	2%
ALT (M: >215 U/L) (F: >170 U/L)	2%	2%

	EMTRIVA+VIREAD+EFV N=257	AZT/3TC+EFV N=254
Hemoglobin (<8.0 mg/dL)	0%	3%
Hyperglycemia (>250 mg/dl)	1%	1%
Hematuria (>75 RBC/HPF)	2%	2%
Neutrophil (>750/mm ³)	3%	4%
Fasting Triglycerides (>750 mg/dL)	4%	2%

Laboratory abnormalities in patients who received treatment up to 144 weeks in Study 934 were consistent with those observed in the first 48 weeks of treatment.

In addition to the events described above for Study 934, other adverse events that occurred in at least 3-5% of patients receiving EMTRIVA or VIREAD with other antiretroviral agents in clinical trials include: anorexia, anxiety, arthralgia, asthenia, increased cough, depressive disorders, dyspepsia, fever, flatulence, myalgia, pain, abdominal pain, back pain, chest pain, paresthesia, peripheral neuropathy (including peripheral neuritis and neuropathy), pneumonia, rhinitis and rash event (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash and allergic reaction), sweating and weight loss.

Skin discoloration has been reported with higher frequency among EMTRIVA treated patients. Skin discoloration, mainly manifested by hyperpigmentation on the palms and/or soles was generally mild and asymptomatic and of little clinical significance. The mechanism is unknown.

In addition to the laboratory abnormalities described above for Study 934, Grade 3/4 elevations of bilirubin (>2.5 x ULN), pancreatic amylase (>2.0 x ULN), serum glucose (<40 or >250 mg/dL), serum lipase (>2.0 x ULN), and urine glucose (≥3+) occurred in up to 3% of patients treated with EMTRIVA or VIREAD with other antiretroviral agents in clinical trials.

For more information, please consult the EMTRIVA and VIREAD Product Monographs.

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 in the VIREAD group compared with patients in the stavudine group (see Table 4). 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. 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.

Table 4 Changes in Bone Mineral Density Study 903

	Mean Percent Change (\pm SD) to Week 144 in BMD	
	VIREAD + 3TC+ EFV	d4T + 3TC +EFV
Lumbar Spine	-2.2% \pm 3.9	-1.0% \pm 4.6
Hip	-2.8% \pm 3.5	-2.4% \pm 4.5

Post Market Adverse Drug Reactions

EMTRIVA: The following adverse experiences have been reported in post-marketing experience without regard to causality. Because these events are voluntarily reported from a population of unknown size, estimates of frequency cannot be made.

- Blood and lymphatic system disorders:* Thrombocytopenia
- Gastrointestinal disorders:* Pancreatitis
- General disorders and administrative site conditions:* Pyrexia
- Metabolism and nutrition disorders:* Lactic acidosis

VIREAD: The following adverse reactions have been identified during post-approval use of VIREAD. Because these events have been reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been considered possible adverse reactions due to a combination of their seriousness, frequency of reporting or potential causal relationship with VIREAD.

- 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
- Blood and lymphatic system disorders:* Thrombocytopenia

<i>Hepatobiliary disorders:</i>	Hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT, GGT)
<i>Skin and Subcutaneous Tissue Disorders:</i>	Rash
<i>Musculoskeletal and Connective Tissue Disorders:</i>	Rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), muscular weakness, myopathy
<i>Renal and urinary disorders:</i>	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
<i>General Disorders and Administration Site Conditions</i>	Asthenia

The following adverse reactions, listed under the body system headings above sometimes appeared to be concurrent with proximal renal tubulopathy: rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), hypokalemia, muscular weakness, myopathy, hypophosphatemia.

There have been three post marketing reports of acute renal failure in patients on concomitant NSAIDS therapy where a relationship to VIREAD could not be excluded. These events mostly occurred in medically complex patients, where underlying disease processes confound interpretation.

VIREAD and EMTRIVA: In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy an inflammatory reaction to infectious pathogens (active or inactive) may arise (see **WARNINGS and PRECAUTIONS**).

In HIV infected patients coinfecting with HBV, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of treatment (See **WARNINGS AND PRECAUTIONS**).

DRUG INTERACTIONS

Drug-Drug Interactions

Serious Drug Interactions

- **Atazanavir and lopinavir/ritonavir increase tenofovir disoproxil fumarate concentrations which may lead to tenofovir-associated adverse events (see **WARNINGS and PRECAUTIONS**)**

Table 5 Drug Interactions: Changes in Pharmacokinetic Parameters for Emtricitabine in the Presence of the Coadministered Drug¹

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 × 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

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

Table 6 Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Emtricitabine¹

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 × 7 days	200 once daily × 7 days	17	↔	↔	↔
Zidovudine	300 twice daily × 7 days	200 once daily × 7 days	27	↑ 17 (↑ 0 to ↑ 38)	↑ 13 (↑ 5 to ↑ 20)	↔
Indinavir	800 × 1	200 × 1	12	↔	↔	NA
Famciclovir	500 × 1	200 × 1	12	↔	↔	NA
Stavudine	40 × 1	200 × 1	6	↔	↔	NA

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

Table 7 Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir¹ 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
Atazanavir ³	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 (↑ 26 to ↑ 38)	↑ 51 (↑ 32 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)	↔	↔

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

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 ¹ (90% CI)		
			C _{max}	AUC	C _{min}
Abacavir	300 once	8	↑ 12 (↓ 1 to ↑ 26)	↔	NA
Atazanavir ²	400 once daily × 14 days	34	↓ 21 (↓ 27 to ↓ 14)	↓ 25 (↓ 30 to ↓ 19)	↓ 40 (↓ 48 to ↓ 32)
Atazanavir ²	Atazanavir/Ritonavir 300/100 once daily × 42 days	10	↓ 28 (↓ 50 to ↑ 5)	↓ 25 ³ (↓ 42 to ↓ 3)	↓ 23 ³ (↓ 46 to ↑ 10)
Efavirenz	600 once daily × 14 days	30	↔	↔	↔
Emtricitabine	200 once daily × 7 days	17	↔	↔	↔
Entecavir	1 mg once daily × 10 days	28	↔	↑ 13 (↑ 11 to ↑ 15)	↔
Indinavir	800 three times daily × 7 days	12	↓ 11 (↓ 30 to ↑ 12)	↔	↔
Lamivudine	150 twice daily × 7 days	15	↓ 24 (↓ 34 to ↓ 12)	↔	↔
Lopinavir Ritonavir	Lopinavir/Ritonavir 400/100 twice daily × 14 days	24	↔	↔	↔
Methadone ⁴	40-110 once daily × 14 days ⁵	13	↔	↔	↔
Nelfinavir M8 metabolite	1250 twice daily × 14 days	29	↔ ↔	↔ ↔	↔ ↔
Oral Contraceptives ⁶	Ethinyl Estradiol/ Norgestimate (Ortho- Tricyclen®) Once daily × 7 days	20	↔	↔	↔
Ribavirin	600 once	22	↔	↔	NA
Saquinavir Ritonavir	1000/100 twice daily × 14 days	32	↑ 22 (↑ 6 to ↑ 41) ↔	↑ 29 ⁷ (↑ 12 to ↑ 48) ↔	↑ 47 ⁷ (↑ 23 to ↑ 76) ↑ 23 (↑ 3 to ↑ 46)
Tacrolimus	0.05 mg/kg twice daily × 7 days	21	↔	↔	↔

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.
7. 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.

Didanosine

Pharmacokinetic studies have shown that coadministration of didanosine and tenofovir disoproxil fumarate results in 40-60% increase in C_{max} and AUC of didanosine (see Table 9). The mechanism of this interaction is unknown. **Increases in didanosine concentrations of this magnitude could potentiate didanosine-associated adverse events, including pancreatitis, lactic acidosis, and neuropathy.** In addition, suppression of CD4 counts has been observed in patients receiving tenofovir disoproxil fumarate with didanosine at a dose of 400 mg daily.

A reduced dose of Videx EC[®] (ddI-EC) is recommended when coadministered with TRUVADA. When coadministered with TRUVADA, the Videx EC[®] Product Monograph recommends a reduced dose of 250 mg ddI-EC for HIV infected adults with body weight ≥60 kg and creatinine clearance ≥60 mL/min. For patients with body weight <60 kg, and creatinine clearance ≥60 mL/min, the recommended dose of ddI-EC is 200 mg. Data are not available to recommend a dose adjustment for patients with creatinine clearance <60mL/min or for the buffered tablet formulation of didanosine (Videx[®]).

Caution should be used when coadministering reduced-dose didanosine, tenofovir, and an NNRTI in treatment-naïve patients with high viral loads at baseline since such use has been associated with reports of a high rate of virologic failure and emergence of resistance at an early stage. All patients receiving tenofovir disoproxil fumarate and didanosine concomitantly should be closely monitored for didanosine-related adverse events and clinical response.

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

Didanosine ¹ Dose (mg)/ Method of Administration ²	Tenofovir Method of Administration ²	N	% Difference (90% CI) vs. Didanosine 400 mg Alone, Fasted ³	
			C _{max}	AUC
Buffered tablets				
400 once daily ⁴ × 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.

Drug-Food Interactions

Interactions of TRUVADA with food have not been established (see ACTIONS AND CLINICAL PHARMACOLOGY, Effect of Food on Absorption).

Drug-Herb Interactions

Interactions of TRUVADA with herbs have not been established.

Drug-Laboratory Interactions

Interactions of TRUVADA with laboratory tests have not been established.

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 **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Insufficiency**). Therefore, the dosing interval of TRUVADA should be adjusted in patients with baseline creatinine clearance 30–49 mL/min using the recommendations in Table 10. These dosing interval recommendations are based on modeling of single-dose pharmacokinetic data in non-HIV infected subjects with varying degrees of renal impairment, including end-stage renal disease requiring hemodialysis. The safety and effectiveness of these dosing interval adjustment recommendations have not been clinically evaluated in moderate to severe renal impairment, therefore, clinical response to treatment and renal function should be closely monitored in these patients. Routine monitoring of creatinine clearance and serum phosphorus should be performed for patients with mild renal impairment (creatinine clearance 50-80 mL/min). (see **WARNINGS and PRECAUTIONS**).

Table 10 Dosage Adjustment for Patients with Altered Creatinine Clearance

	Creatinine Clearance (mL/min) ¹		
	≥50	30–49	<30 (Including Patients Requiring Hemodialysis)
Recommended Dosing Interval	Every 24 hours	Every 48 hours	TRUVADA should not be administered.

1. Calculated using ideal (lean) body weight.

Missed Dose

If a patient misses a dose at the regularly scheduled time, but then remembers it that same day, the patient should take the missed dose immediately. The patient should not take more than 1 dose of TRUVADA in a day, or 2 doses of TRUVADA at the same time to make up for missing a dose.

OVERDOSAGE

For management of a suspected drug overdose, please contact your regional Poison Control Centre.

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. The effects of higher doses are not known.

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), however, a single treatment does not significantly affect emtricitabine C_{max} or AUC. 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. 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.

ACTION AND CLINICAL PHARMACOLOGY

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 polymerases 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 .

Pharmacodynamics

Antiviral Activity In Vitro

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 IC₅₀ (50% inhibitory concentration) 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, and zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, and nevirapine), and protease inhibitors (amprenavir, nelfinavir, ritonavir, and 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 (IC₅₀ values ranged from 0.007–0.075 μM) and showed strain specific activity against HIV-2 (IC₅₀ 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 IC₅₀ 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, and zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, and nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, and saquinavir), additive to synergistic effects were observed. Most of these drug combinations have not been studied in humans. Tenofovir displayed antiviral activity in vitro against HIV-1 clades A, B, C, D, E, F, G, and O (IC₅₀ values ranged from 0.5–2.2 μM).

Antiviral Activity In Vivo

The antiviral effects of emtricitabine and tenofovir disoproxil fumarate in terms of reducing HIV-1 viral load and the relationship with dose were assessed in clinical phase 1 studies in treatment-naïve and treatment-experienced HIV-infected patients.

Emtricitabine: The in vivo activity of emtricitabine was evaluated in two clinical trials in which 101 patients were administered 25 to 400 mg a day of EMTRIVA as monotherapy for 10 to 14 days. A dose-related antiviral effect was observed, with a median decrease from baseline in plasma HIV-1 RNA of 1.3 log₁₀ at a dose of 25 mg QD and 1.7 log₁₀ to 1.9 log₁₀ at a dose of 200 mg QD or BID.

Tenofovir disoproxil fumarate: The antiviral effects of tenofovir disoproxil fumarate monotherapy in reducing HIV-1 viral load and the relationship with dose were assessed in clinical phase 1 studies in treatment-naïve and treatment-experienced HIV-infected patients. Doses of tenofovir disoproxil fumarate ranging from 75 mg to 600 mg once daily resulted in statistically significant decreases in plasma HIV-1 RNA levels compared with placebo. In a mixed population of treatment-naïve and treatment-experienced patients who received 28 days of repeat daily dosing with tenofovir disoproxil fumarate 300 mg QD (Study GS-97-901) the median decrease in plasma log₁₀ HIV-1 RNA level was 1.22 log₁₀ copies/mL.

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 11. 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 11. 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 11 Single Dose Pharmacokinetic Parameters for Emtricitabine and Tenofovir in Adults

	Emtricitabine	Tenofovir
Fasted Oral Bioavailability ² (%)	92 (83.1–106.4)	25 (NC–45.0) ¹
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 and Conditions

Pediatrics and Geriatrics

Pharmacokinetics of emtricitabine and tenofovir have not been fully evaluated in children (<18 years) or in the elderly (>65 years).

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.

Gender

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

Hepatic Insufficiency

The pharmacokinetics of tenofovir following a 300 mg single 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 patients with hepatic impairment; however, emtricitabine has not been shown to be significantly metabolized by liver enzymes, so the impact of liver impairment is likely to be limited.

Renal Insufficiency

The pharmacokinetics of emtricitabine and tenofovir are altered in patients with renal insufficiency (see **WARNINGS, Nephrotoxicity**). 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 **DOSAGE AND ADMINISTRATION**).

STORAGE AND STABILITY

Store at 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.

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

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), 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, hydropropylmethylcellulose 2910, lactose monohydrate, titanium dioxide, and triacetin. 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 and a desiccant (silica gel canister or sachet) and is closed with a child-resistant closure.

PART II. SCIENTIFIC INFORMATION

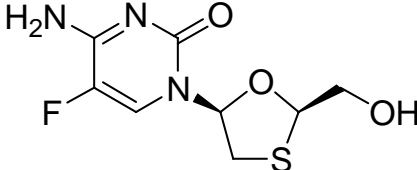
PHARMACEUTICAL INFORMATION

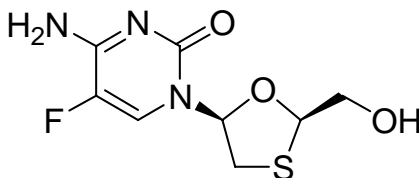
TRUVADA Tablets are fixed dose combination tablets containing emtricitabine and tenofovir disoproxil fumarate. EMTRIVA is the brand name for emtricitabine, a synthetic nucleoside analog of cytidine. Tenofovir disoproxil fumarate (VIREAD, also known as tenofovir DF) is converted in vivo to tenofovir, 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.

Drug Substance

Emtricitabine:

Common Name:	emtricitabine (USAN)
Chemical Name:	5-fluoro-1-(2R,5S)-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine
Empirical Formula:	C ₈ H ₁₀ FN ₃ O ₃ S
Molecular Weight:	247.24
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:

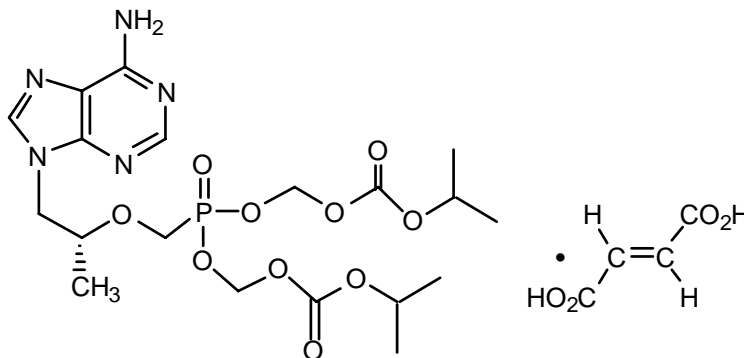
Common Name: tenofovir disoproxil fumarate (USAN)

Chemical Name: 9-[(R)-2-[[bis[[[isopropoxycarbonyl]oxy]methoxy]phosphinyl]-methoxy]propyl]adenine fumarate (1:1)

Empirical Formula: C₁₉H₃₀N₅O₁₀P • C₄H₄O₄

Molecular Weight: 635.52

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.

CLINICAL TRIALS

Study Demographics and Trial Design

Description of Clinical Studies

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

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 were used in combination in treatment-naïve adults, and clinical Study 303 in which EMTRIVA and lamivudine demonstrated comparable efficacy, safety and resistance patterns as part of multidrug regimens (see Table 16 and Table 17).

Table 12 Study 934 EMTRIVA + VIREAD + Efavirenz Compared with Lamivudine/Zidovudine + Efavirenz

Study Number	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (N=511)	Mean Age	Gender
GS-01-934	Randomized, open-label, parallel, multicenter, active controlled study. Arm 1: emtricitabine+ tenofovir DF+ efavirenz Arm 2: lamivudine/ zidovudine + efavirenz	Arm 1 ¹ : efavirenz 600 mg once daily for oral administration, emtricitabine 200 mg once and tenofovir DF 300 mg once daily Arm 2: efavirenz 600 mg once daily for oral administration and Combivir (lamivudine/ zidovudine) 150/300 mg twice daily. 144 weeks	Antiretroviral naive patients (HIV-1 RNA > 10,000 copies/mL) (N=511)	Mean 38 years (18–80)	Male : 86% Female: 14%

¹From weeks 96 to 144 of the study, patients received TRUVADA with efavirenz in place of emtricitabine + VIREAD

Data through 144 weeks are reported for Study 934, a randomized, open-label, active controlled multicenter study comparing EMTRIVA + VIREAD administered in combination with efavirenz versus lamivudine/zidovudine administered in combination with efavirenz in 511 antiretroviral-naïve patients. From weeks 96 to 144 of the study, patients randomized to EMTRIVA + VIREAD received TRUVADA with efavirenz in place of EMTRIVA + VIREAD. Patients 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-1RNA was 5.01 log₁₀ copies/mL (range 3.56–6.54). Patients were stratified by baseline CD4 count (< or ≥200 cells/mm³); 41% had CD4 cell counts <200 cells/mm³ and 51% of patients had baseline viral loads >100,000 copies/mL.

EMTRIVA:

Table 13 Study 303: EMTRIVA QD + Stable Background Therapy (SBT) Compared to Lamivudine BID + SBT

Study No.	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (N=440)	Mean Age (Range)	Gender
FTC-303	Randomized (2:1), open-label, active-controlled switch study. Arm 1: emtricitabine + (d4T or ZDV + PI or NNRTI) Arm 2: lamivudine + (d4T or ZDV + PI or NNRTI)	Arm 1: emtricitabine 200 mg capsules orally, QD + (d4T or ZDV + PI or NNRTI) for 48 weeks Arm 2: lamivudine 150 mg tablet orally, BID + (d4T or ZDV + PI or NNRTI) for 48 weeks	Stable treatment-experienced (HIV-1 RNA <400 copies/mL) (N=440)	42 years (22–80)	Male: 86% Female: 14%

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/mm³ (range 37–1909), and a median baseline plasma HIV RNA of 1.7 log₁₀ copies/mL (range 1.7–4.0). The median duration of prior antiretroviral therapy was 27.6 months.

VIREAD:

Table 14 Study 903: VIREAD + Lamivudine + Efavirenz Compared with Stavudine + Lamivudine + Efavirenz

Study No.	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (N=600)	Mean Age (Range)	Gender
GS-99-903	Randomized (1:1), double-blind, active-controlled, equivalence study. Arm 1: tenofovir DF + lamivudine + efavirenz Arm 2: stavudine + lamivudine + efavirenz	Arm 1: tenofovir DF 300 mg tablets QD, stavudine placebo capsules BID, lamivudine 150 mg tablets BID, efavirenz 600 mg QD Arm 2: tenofovir DF placebo tablets QD, stavudine ¹ capsules 40/30 mg BID, lamivudine 150 mg tablets BID, efavirenz 600 mg QD All for oral (PO) administration for 144 weeks double-blind phase followed by 192-week open-label phase. (Nevirapine 200 mg BID could replace efavirenz in the event of efavirenz-associated central nervous system toxicity or rash.)	Treatment-naïve (HIV-1 RNA >5,000 copies/mL) (N=600)	36 years (18–64)	Male: 74% Female: 26%

1. Stavudine/placebo capsules 20/15 mg BID as need for dose reduction.

Study 903 is 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/mm³ (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/mL.

Study Results

EMTRIVA and VIREAD

Study 934: EMTRIVA + VIREAD + Efavirenz Compared with Lamivudine/Zidovudine + Efavirenz

Treatment outcomes through 48 and 144 weeks for those patients who did not have efavirenz resistance at baseline are presented in **Error! Reference source not found.**

Table 15 Outcomes of Randomized Treatment at Weeks 48 and 144 (Study 934)

Outcome	At Week 48		At Week 144 ¹	
	EMTRIVA+ VIREAD +EFV	3TC+AZT +EFV	EMTRIVA+ VIREAD+ EFV	3TC/AZT +EFV
	(N=244)	(N=243)	(N=227)	(N=229)
Responder ²	84%	73%	71%	58%
Virologic failure ³	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 ⁴	10%	14%	20%	22%

1. Patients who were responders at Week 48 or Week 96 but did not consent to continue study after Week 48 or Week 96 were excluded from analysis.
2. Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Week 48.
3. Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Week 48.
4. Includes lost to follow-up, patient withdrawal, non-compliance, protocol violation and other reasons.

In this study, EMTRIVA + VIREAD in combination with efavirenz demonstrated statistically significant superiority to lamivudine/zidovudine in combination with efavirenz in achieving and maintaining HIV-1 RNA <400 copies/mL through 48 weeks and 144 weeks (Table 15). The difference in the percentages of responders, stratified by baseline CD4 cell count (< or ≥200 cells/mm³), between the EMTRIVA + VIREAD group and the lamivudine/zidovudine group was 11.4%, and the 95% CI was 4.3% to 18.6% (p=0.002) at Week 48 and was 13% at Week 144, 95% CI = 4% to 22% (p=0.004). Through 48 weeks of therapy, 80% and 70% of patients in the EMTRIVA + VIREAD and the lamivudine/zidovudine arms, respectively, achieved and maintained HIV-1 RNA <50 copies/mL (64% and 56%, respectively, through Week 144). The difference in the percentages of responders stratified by baseline CD4 cell count (< or ≥200 cells/mm³) between the EMTRIVA + VIREAD group and the lamivudine/zidovudine group was 9.1%,

and the 95% CI was 1.6% to 16.6% (p=0.021) at Week 48 and was 8% at Week 144, 95% CI = -1% to 17% (p=0.082). The mean increase from baseline in CD4 cell count was 190 cells/mm³ for the EMTRIVA + VIREAD + efavirenz arm, and 158 cells/mm³ for the lamivudine/zidovudine + efavirenz arm (p=0.002) at Week 48 (312 and 271 cells/mm³, respectively, at Week 144, p=0.089).

The difference in the proportion of patients 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 study.

EMTRIVA:

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

Treatment outcomes through 48 weeks are presented in Table 16.

Table 16 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/mm³ for the EMTRIVA arm and 61 cells/mm³ 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

Treatment outcomes at Week 48 and Week 144 are presented in Table 17 below.

Table 17 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% (76%)	82% (79%)	68% (62%)	62% (58%)
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 (<50 copies/mL) at Weeks 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.

Through 48 weeks, the mean increase from baseline in CD4 cell count was 169 cells/mm³ for the VIREAD arm and 167 cells/mm³ for the stavudine arm. Eight patients in the VIREAD group and six patients in the stavudine group experienced a new CDC Class C event.

Through 144 weeks, the mean increase from baseline in CD4 cell count was 263 cells/mm³ for the VIREAD arm and 283 cells/mm³ for the stavudine arm. Eleven patients in the VIREAD group and nine patients in the stavudine group experienced a new CDC Class C event.

Comparative Bioavailability Studies

Study GS-US-104-0172 was a single-dose, randomized, open-label, four-treatment, single center, four-way crossover study conducted in healthy male and healthy, nonpregnant, nonlactating female volunteers to establish biocomparability between the combination tablet (containing 200 mg emtricitabine/300 mg tenofovir disoproxil fumarate) and concurrent administration of the 200 mg capsule of emtricitabine and the 300 mg tablet of tenofovir disoproxil fumarate under fasting conditions by evaluation of C_{max} and AUC of emtricitabine and tenofovir. In addition, this study was conducted to investigate the effect of food (high fat and light meal) on the pharmacokinetics of the combination tablet. Study GS-US-104-0172 biocomparability results are summarized in Table 18 and Table 19 below. A summary of the food effect analysis of Study GS-US-104-0172 is found in **ACTION AND CLINICAL PHARMACOLOGY, Effects of Food on Oral Absorption**.

Table 18 Summary of Emtricitabine Pharmacokinetic Parameters (GS-US-104-0172) – Fasted

Emtricitabine 200mg From Measured Data				
Geometric Mean				
Arithmetic Mean (CV%)				
Parameter	Test Treatment B ² (N=39)	Reference Treatment A ¹ (N=38)	% Ratio of Geometric Means	90% Confidence Interval
AUC _T (µg•h/mL)	10.10 10.32 (20.68)	10.17 10.39 (20.12)	100.1	95.9–104.5
AUC ₁ (µg•h/mL)	10.41 10.62 (20.21)	10.47 10.70 (20.01)	100.2	96.2–104.4
C _{max} (µg/mL)	2.03 2.13 (28.36)	2.13 2.21 (26.73)	96.5	89.5–104.0
T _{max} ³ (h)	1.50 (0.75–3.0)	1.25 (0.75–3.0)		
T _½ ⁴ (h)	15.64 (23.32)	15.31 (24.96)		

1. Treatment A=concurrent administration of a 200 mg capsule of emtricitabine (Emtriva manufactured by Abbott Laboratories, Abbott Park, IL, USA for Gilead Sciences, Inc.) and a 300 mg tablet of tenofovir disoproxil fumarate (Viread manufactured by Patheon Inc., Mississauga, ON, Canada for Gilead Sciences, Inc.) to fasted subjects.
2. Treatment B=200 mg emtricitabine/300 mg tenofovir disoproxil fumarate combination tablet (Truvada manufactured by Patheon Inc., Mississauga, ON, Canada for Gilead Sciences, Inc.) administered to fasted subjects.
3. Expressed as the median (range) only.
4. Expressed as the arithmetic mean (CV%) only.

Table 19 Summary of Tenofovir Pharmacokinetic Parameters (GS-US-104-0172) – Fasted

Tenofovir 300mg From Measured Data Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test Treatment B ² (N=39)	Reference Treatment A ¹ (N=39)	% Ratio of Geometric Means	90% Confidence Interval
AUC _T (ng•h/mL)	1500.94 1605.84 (33.28)	1502.83 1593.06 (29.16)	100.0	94.0–106.5
AUC _I (ng•h/mL)	1848.94 1961.07 (30.31)	1845.31 1944.98 (26.23)	100.3	94.6–106.3
C _{max} (ng/mL)	240.36 253.63 (32.91))	255.61 267.59 (30.13)	94.0	85.8–103.0
T _{max} ³ (h) ³	0.75 (0.50–2.50)	0.75 (0.50–2.50)		
T _½ ⁴ (h)	16.48 (25.02)	17.51 (24.07)		

1. Treatment A=concurrent administration of a 200 mg capsule of emtricitabine (Emtriva manufactured by Abbott Laboratories, Abbott Park, IL, USA for Gilead Sciences, Inc.) and a 300 mg tablet of tenofovir disoproxil fumarate (Viread manufactured by Patheon Inc., Mississauga, ON, Canada for Gilead Sciences, Inc.) to fasted subjects.
2. Treatment B=200 mg emtricitabine/300 mg tenofovir disoproxil fumarate combination tablet (Truvada manufactured by Patheon Inc., Mississauga, ON, Canada for Gilead Sciences, Inc.) administered to fasted subjects.
3. Expressed as the median (range) only.
4. Expressed as the arithmetic mean (CV%) only.

DETAILED PHARMACOLOGY

VIROLOGY (MICROBIOLOGY)

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 polymerases 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 IC₅₀ 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, and zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, and nevirapine), and protease inhibitors (amprenavir, nelfinavir, ritonavir, and 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 (IC₅₀ values ranged from 0.007–0.075 μM) and showed strain specific activity against HIV-2 (IC₅₀ 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 IC₅₀ (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, and zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, and nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, and saquinavir), additive to synergistic effects were observed. Most of these drug combinations have not been studied in humans. Tenofovir displayed antiviral activity in vitro against HIV-1 clades A, B, C, D, E, F, G, and O (IC₅₀ values ranged from 0.5–2.2 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 M184V/I and/or K65R amino acid substitutions in the viral RT.

In Study 934 (EMTRIVA + VIREAD + efavirenz compared with lamivudine/zidovudine + efavirenz), resistance analysis was performed on HIV isolates from all patients with >400 copies/mL of HIV-1 RNA at Week 144 or early discontinuation. Genotypic resistance to efavirenz, predominantly the K103N mutation, was the most common form of resistance that developed. Resistance to efavirenz occurred in 13/19 (68%) analyzed patients in the EMTRIVA + VIREAD group and in 21/29 (72%) analyzed patients in the lamivudine/zidovudine group. The M184V mutation, associated with resistance to EMTRIVA and lamivudine, was observed in 2/19 (11%) analyzed patients in the EMTRIVA + VIREAD group and in 10/29 (34%) analyzed patients in the lamivudine/zidovudine group.

In treatment-naïve patients treated with EMTRIVA + VIREAD + efavirenz, none of the HIV isolates from 19 patients analyzed for resistance showed reduced susceptibility to tenofovir or the presence of the K65R mutation.

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, 7/29 (24%) isolates from patients failing VIREAD + lamivudine + efavirenz at 48 weeks showed >1.4 fold (median 3.4) reduced susceptibility in vitro to tenofovir.

In treatment-experienced patients, 14/304 (4.6%, studies 902 and 907) isolates from patients failing VIREAD at 96 weeks 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.

TOXICOLOGY

Carcinogenesis

Emtricitabine: In long-term oral carcinogenicity studies of emtricitabine, no drug-related increase in tumor incidence was 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).

Tenofovir disoproxil fumarate: Long-term oral carcinogenicity studies were conducted in mice and rats receiving tenofovir disoproxil fumarate. In the mouse study, (60/sex/group), one male and two female mice in the 600 mg/kg/day group (15 times the human systemic exposure at the recommended human dose of 300 mg/day) had duodenal tumors. The mechanism underlying this effect is uncertain but may relate to high local drug concentrations in the gastrointestinal tract. No treatment-related tumors were seen in mice in the 100 or 300 mg/kg/day groups. In the rat study (60/sex/group) at doses of 30, 100, and 300 mg/kg/day (approximately 5 times human exposure), no treatment-related increase in tumor incidence was observed.

Mutagenesis

Emtricitabine: Emtricitabine was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or mouse micronucleus assays.

Tenofovir disoproxil fumarate: Tenofovir disoproxil fumarate was negative in the in vitro bacterial mutation (Ames) assay (*Salmonella-Eschericia coli*/Mammalian-Microsome Reverse Mutation Assay) but positive in the in vitro mouse lymphoma assay (L5178Y TK +/- Forward Mutation Assay), with and without metabolic activation. Tenofovir disoproxil fumarate was negative in the in vivo mouse micronucleus assay at plasma exposure levels of more than 10× the human exposure.

Impairment of Fertility

Emtricitabine: 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: Reproductive toxicity was evaluated in rats and rabbits. Tenofovir disoproxil fumarate had no adverse effects on fertility or general reproductive performance in rats at doses up to 600 mg/kg/day. Tenofovir disoproxil fumarate had no adverse effects on embryo-fetal development in rats at doses 450 mg/kg/day and in rabbits at doses up to 300 mg/kg/day. In a study of effects on peri- and postnatal development in rats, effects considered due to maternal toxicity (450–600 mg/kg/day) were reduced survival and a slight delay in sexual maturation in the F1 generation. There were no adverse effects on growth, development, behavior, or reproductive parameters at non-maternally toxic doses (150 mg/kg/day).

Pregnancy

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. Reduced pup body weights, survival and delay in sexual maturation was observed in a peri- and postnatal toxicity study in rats at the maternally toxic doses of 450 and 600 mg/kg (approximately 14 and 19 times the human dose based on body surface area comparisons).

Antiretroviral Pregnancy Registry

To monitor fetal outcomes of pregnant women exposed to ART (antiretroviral therapy) including TRUVADA, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients by calling 800–258–4263.

REFERENCES

1. Deeks SG, Barditch-Crovo P, Lietman PS, Hwang F, Cundy KC, Rooney JF, et al. Safety, pharmacokinetics, and antiretroviral activity of intravenous 9-[2-(R)-(phosphonomethoxy)propyl]adenine, a novel anti-human immunodeficiency virus (HIV) therapy, in HIV-infected adults. *Antimicrob Agents Chemother* 1998 Sep;42 (9):2380-4.
2. Barditch-Crovo P, Deeks SG, Collier A, Safrin S, Coakley DF, Miller M, et al. Phase I/II trial of the pharmacokinetics, safety, and antiretroviral activity of tenofovir disoproxil fumarate in HIV-1 infected adults. *Antimicrob Agents Chemother* 2001 Oct;45 (10):2733-9.
3. Schooley RT, Ruane P, Myers RA, Beall G, Lampiris H, Berger D, et al. Tenofovir DF in antiretroviral-experienced patients: results from a 48-week, randomized, double-blind study. *AIDS* 2002 Jun 14;16 (9):1257-63.
4. Margot NA, Isaacson E, McGowan I, Cheng AK, Schooley RT, Miller MD. Genotypic and phenotypic analyses of HIV-1 in antiretroviral-experienced patients treated with tenofovir DF. *AIDS* 2002 Jun 14;16 (9):1227-35.
5. Koutsavlis, AT., Toole, J. Bristol-Myers Squibb Canada and Gilead Sciences letter to physicians about clinical data: Important Information Pertaining to the Coadministration of Videx[®] and Viread. June 9, 2005.
6. Gallant, J.E., DeJesus, E., Arribas, J.R., Pozniak, A.L., Gazzard, B., Campo, R.E. et al. Tenofovir DF, Emtricitabine and Efavirenz versus Zidovudine, Lamivudine and Efavirenz for HIV. *New Engl. J. Med.* 2006 (354): 251-260.
7. EMEA Public Statement, Efficacy and safety concerns regarding the co-administration of tenofovir disoproxil fumarate (TDF, Viread) and didanosine (ddI, Videx), 2005. <http://www.emea.eu.int/pdfs/human/press/pus/6233105en.pdf>
8. Podzamczer D, Ferrer E, Gatell JM, Niubo J, Dalmau D, Leon A, Knobel H, Polo C, Iniguez D, Ruiz I. Early virological failure with a combination of tenofovir, didanosine and efavirenz. *Antiviral Therapy* 2005; 10: 171-177

PART III. CONSUMER INFORMATION

Pr **Truvada**[®]

(Emtricitabine/Tenofovir Disoproxil Fumarate Tablets)

This leaflet is Part III of a three part “Product Monograph” published when TRUVADA was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about TRUVADA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

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.

What it does:

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). Lowering the amount of HIV in the blood lowers the chance of infections that happen when your immune system is weak (opportunistic infections).

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 may also help to increase the number of T cells (CD4 cells).

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) infections. **It is very important that you see your doctor regularly while taking TRUVADA.**

TRUVADA does not reduce the risk of passing HIV to others through sexual contact or blood contamination. Continue to practice safe sex and do not use or share dirty needles.

When it should not be used:

Together with your doctor, you need to **decide** whether TRUVADA is right for you.

Do not take TRUVADA if:

- you are on other medications that may affect your kidneys and have not discussed this with your doctor

- you have or are at known risk for any type of bone disease or bone related problems and have not discussed this with your doctor
- you are allergic to TRUVADA or any of its ingredients. The medicinal ingredients are emtricitabine and tenofovir DF (**See What the important nonmedicinal ingredients in TRUVADA are**).
- you are already taking ATRIPLA[®], Combivir[®], EMTRIVA, 3TC[®], Heptovir[®], Kivexa[™], Trizivir[®], or VIREAD, because these medicines contain the same or similar active ingredients
- you are also taking HEPSERA[®] to treat your HBV infection

What the medicinal ingredients are:

emtricitabine
tenofovir disoproxil fumarate (tenofovir DF)

What the important nonmedicinal ingredients are:

croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch, FD&C blue #2, hypromellose, titanium dioxide and triacetin.

What dosage forms it comes in:

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), as active ingredients. 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 and a desiccant (silica gel canister or sachet) and is closed with a child-resistant closure.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- The most serious possible side effect is harm to the kidneys, including damage to kidney cells, kidney tissue inflammation and kidney failure. Your doctor may monitor your kidney function before beginning and while receiving TRUVADA. Some patients treated with tenofovir disoproxil fumarate (a component of TRUVADA) have had kidney problems. Your doctor may need to perform additional blood tests if you have had kidney problems in the past or need to take another drug that can cause kidney problems.
- **If you are also infected with the Hepatitis B Virus, “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. Do not stop taking TRUVADA without your doctor’s advice. If you stop taking TRUVADA, tell your doctor immediately about any new, unusual or worsening symptoms that you notice after stopping treatment. After you stop taking TRUVADA, your doctor will still need to check your health and take blood tests to check your liver for several months. TRUVADA is not approved for the treatment of Hepatitis B Virus infection.
- The class of medicines to which TRUVADA belong (NRTIs) can cause a condition called lactic acidosis,

together with an enlarged liver. Non-specific symptoms such as nausea, vomiting and stomach pain might indicate the development of lactic acidosis. This rare but serious side effect has occasionally been fatal. Lactic acidosis occurs more often in women, particularly if they are very overweight. You should consult your doctor immediately if such symptoms occur while you are receiving TRUVADA. The symptoms that may indicate a liver problem include: feeling very weak, tired or uncomfortable; unusual or unexpected stomach discomfort; feeling cold; feeling dizzy or lightheaded; suddenly developing a slow or irregular heartbeat. If you notice these symptoms, stop taking TRUVADA and consult a doctor immediately.

- Tenofovir disoproxil fumarate caused harm to the bones of animals. Tenofovir disoproxil fumarate reduced bone density in humans. If you notice bone pain, suffer a bone fracture, or other bone problem, consult your doctor. If you have bone problems, you may wish to discuss calcium and/or vitamin D supplements with your doctors.
- Changes in body fat have been seen in some patients taking antiretroviral therapy. These changes may include increased amounts of fat in the upper back and neck (“buffalo hump”), breast, and around the trunk. Loss of fat from the legs, arms and face may also happen. The cause and long term health effects of these conditions are not known at this time.

If you have advanced HIV infection (AIDS) and have an infection, you may develop symptoms of infection and inflammation or worsening of the symptoms of an existing infection once treatment with Truvada is started. These symptoms may indicate that your body’s improved immune system is fighting infection. If you notice signs of inflammation or infection, tell your doctor at once.

BEFORE you use TRUVADA (emtricitabine / tenofovir disoproxil fumarate) talk to your doctor or pharmacist:

If you are pregnant or planning to become pregnant: The effects of TRUVADA on pregnant women or their unborn babies are not known. Your doctor will advise whether you should take TRUVADA.

If you are breast-feeding: Do not breast-feed if you are taking TRUVADA. Do not breast-feed if you have HIV. If you are a woman who has or will have a baby, talk with your doctor about the best way to feed your baby. If your baby does not already have HIV, there is a chance that the baby can get HIV through breast-feeding.

If you have other medical conditions: Let your doctor know if you have other medical conditions, especially liver, bone and kidney problems.

If you are taking other medicines: Some medicines can interact when taken together, including prescription and non-prescription

medicines and dietary supplements (see **INTERACTIONS WITH THIS MEDICATION**).

It is a good idea to 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 every time you visit your doctor or fill a prescription.

INTERACTIONS WITH THIS MEDICATION

Let your doctor know if you are taking these or any other medications:

- Drugs that contain didanosine (Videx[®], Videx EC[®]). Tenofovir disoproxil fumarate (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).

PROPER USE OF THIS MEDICATION

Stay under a doctor’s care when taking TRUVADA. Do not change your treatment or stop treatment without first talking with your doctor.

Take TRUVADA exactly as your doctor prescribed it. Follow the directions from your doctor, exactly as written on the label. Set up a dosing schedule and follow it carefully.

When your TRUVADA supply starts to run low, get more from your doctor 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.

Only take medicine that has been prescribed specifically for you. Do not give TRUVADA to others or take medicine prescribed for someone else.

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

Usual Adult Dose:

- The usual dose of TRUVADA is one tablet orally (by mouth) once a day, in combination with other anti-HIV medicines.
- TRUVADA may be taken with or without a meal.

Overdosage:

If you suspect that you took more than the prescribed dose of TRUVADA, contact your local poison control center or emergency room right away. As with all medicines, TRUVADA should be kept out of reach of children.

Missed Dose:

It is important that you do not miss any doses. If you miss a dose of 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 doctor or pharmacist if you are not sure what to do.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects of EMTRIVA and VIREAD are:

- Diarrhea
- Nausea
- Vomiting
- Dizziness
- Headache

Other side effects include:

- Stomach pain
- Indigestion
- Inflammation of the pancreas
- Sleeping problems
- Abnormal dreams
- Weakness
- Pain
- Shortness of breath
- Allergic reaction (including swelling of the face, lips, tongue or throat)
- Rash
- Flatulence (intestinal gas)
- Skin discoloration (small spots or freckles) may also happen with TRUVADA

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / Effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Rare	Effect: Kidney problems Symptoms		
	• You may have increased or decreased urination as well as increased thirst	✓	
	• You may have swelling of your legs and feet	✓	
	• You may feel listless and tired	✓	

Rare	Effect: Lactic acidosis Symptoms			
	• Feeling very weak or tired		✓	
	• Unusual muscle pain		✓	
	• Stomach pain with nausea and vomiting		✓	
	• Feeling cold especially in arms and legs		✓	
	• Feeling dizzy or lightheaded		✓	
	• Fast or irregular heartbeat		✓	
Very Rare	Effect: Hepatotoxicity (severe liver problems) with hepatomegaly (liver enlargement) and steatosis (fat in the liver) Symptoms			
	• Jaundice (skin or the white part of eyes turn yellow)		✓	
	• Urine turns dark		✓	
	• Bowel movements (stools) turn light in color		✓	
	• Loss of appetite for several days or longer		✓	
	• Feeling sick to your stomach (nausea)		✓	
	• Lower stomach pain		✓	
Very Rare	Effect: Flare-ups of hepatitis B virus infection following drug discontinuation Symptoms			
	• Jaundice (skin or the white part of eyes turn yellow)		✓	
	• Urine turns dark		✓	
	• Bowel movements (stools) turn light in color		✓	
	• Loss of appetite for several days or longer		✓	
	• Feeling sick to your stomach (nausea)		✓	
	• Lower stomach pain		✓	

Lactic acidosis is a medical emergency and must be treated in the hospital. You may be more likely to get lactic acidosis or serious liver problems if you are very overweight (obese) or have been taking nucleoside analog medicines, like TRUVADA, for a long time.

Muscle pain, muscle weakness, bone pain and softening of the bone (infrequently contributing to fractures) have also been reported.

There have been other side effects in patients taking EMTRIVA or VIREAD. *This is not a complete list of side effects.* If you have questions about side effects, ask your doctor, nurse, or pharmacist. You should report any new or continuing symptoms to your doctor right away. Your doctor may be able to help you manage these side effects.

HOW TO STORE IT

- Keep TRUVADA and all other medications out of reach of children.
- TRUVADA should be stored at 15–30 °C (59–86 °F). It should remain stable until the expiration date printed on the label.
- Do not keep your medicine in places that are too hot or cold.
- 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.
- Keep TRUVADA in its original container and keep the container tightly closed.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701C
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the Medeffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health care professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be found at:

www.gilead.ca

or by contacting the sponsor, Gilead Sciences, Inc., at:

1–866–207–4267

This leaflet was prepared by Gilead Sciences, Inc.

Last revised: May 2009

Gilead Sciences, Inc.
Foster City, CA 94404
USA

Gilead Sciences Canada, Inc.
Mississauga, ON
L5N 2W3

TRUVADA, VIREAD, EMTRIVA and HEPSERA are registered trademarks of Gilead Sciences, Inc. or its related companies.

ATRIPLA is a registered trademark of Bristol-Myers Squibb and Gilead Sciences, LLC.

All other trademarks referenced herein are the property of their owners.

© 2009 Gilead Sciences, Inc. All rights reserved.



GS9427-G0701-30-010