

Emtricitabine and Tenofovir Disoproxil Fumarate Tablets

Tenvir-EM

WARNING

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

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGS, INCLUDING TENOFOVIR, A COMPONENT OF TENVIR-EM, IN COMBINATION WITH OTHER ANTIRETROVIRALS (SEE WARNINGS AND PRECAUTIONS).

TENVIR-EM IS NOT APPROVED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION AND THE SAFETY AND EFFICACY OF TENVIR-EM HAVE NOT BEEN ESTABLISHED IN PATIENTS COINFECTED WITH HBV AND HIV-1. SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO ARE COINFECTED WITH HBV AND HIV-1 AND HAVE DISCONTINUED TENOFOVIR/EMTRICITABINE. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO ARE COINFECTED WITH HIV-1 AND HBV AND DISCONTINUED TENVIR-EM. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS AND PRECAUTIONS).

COMPOSITION

TENVIR-EM

Each tablet contains

Emtricitabine200 mg

Tenofovir disoproxil fumarate.....300 mg

Equivalent to tenofovir disoproxil245 mg

DOSAGE FORM

Oral, fixed-dose tablet

PHARMACOLOGY

Pharmacodynamics

Tenofovir disoproxil fumarate (Tenofovir DF): Tenofovir DF is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir DF requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase 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 and β , and mitochondrial DNA polymerase γ .

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 by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into nascent viral DNA, which results in chain termination. Emtricitabine 5'-triphosphate is a weak inhibitor of mammalian DNA polymerase α , β and ϵ and mitochondrial DNA polymerase γ .

Pharmacokinetics in Adults

Tenofovir DF: The pharmacokinetic properties of tenofovir DF are summarized in Table 1. Following oral administration of tenofovir DF, 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 $\mu\text{g/mL}$. 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 tenofovir DF, the terminal elimination half-life of tenofovir is approximately 17 hours.

Emtricitabine: The pharmacokinetic properties of emtricitabine are summarized in Table 1. Following oral administration, 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 $\mu\text{g/mL}$. Following administration of radiolabeled emtricitabine, approximately 86% is recovered in the urine and 13% is recovered as metabolites. The metabolites of emtricitabine include 3'-sulfoxide diastereomers and their glucuronic acid conjugate. Emtricitabine is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of emtricitabine, the plasma emtricitabine half-life is approximately 10 hours.

Table 1: Single Dose Pharmacokinetic Parameters for Emtricitabine and Tenofovir in Adults¹

	Emtricitabine	Tenofovir
Fasted oral bioavailability ² (%)	92 (83.1-106.4)	25 (NC-45.0)
Plasma terminal elimination half-life ² (hr)	10 (7.4-18.0)	17 (12.0-25.7)
C _{max} ³ (µg/mL)	1.8 ± 0.72 ⁴	0.30 ± 0.09
AUC ³ (µg·hr/mL)	10.0 ± 3.12 ⁴	2.29 ± 0.69
CL/F ³ (mL/min)	302 ± 94	1043 ± 115
CL _{renal} ³ (mL/min)	213 ± 89	243 ± 33
¹ .NC = Not calculated ² .Median (range) ³ .Mean (± SD) ⁴ . Data presented as steady state values.		

Effects of Food on Oral Absorption

TENVIR EM may be administered with or without food. Administration of tenofovir/emtricitabine 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 hours. 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, tenofovir was taken under fed conditions. Emtricitabine systemic exposures (AUC and C_{max}) were unaffected when tenofovir/emtricitabine was administered with either a high fat or a light meal.

Special Populations

Race

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

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

Gender

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

Pediatric and Geriatric Patients

Pharmacokinetic studies of tenofovir have not been performed in pediatric patients (<18 years). The pharmacokinetics of emtricitabine and tenofovir has not been fully evaluated in the elderly (>65 years).

Patients with Renal Impairment

The pharmacokinetics of emtricitabine and tenofovir are altered in patients with renal impairment [see **WARNINGS AND PRECAUTIONS**]. In patients with creatinine clearance <50 mL/min, C_{max}, and AUC_{0-∞} of emtricitabine and tenofovir were increased. It is recommended that the dosing interval for **TENVIR EM** be modified in patients with creatinine clearance of 30–49 mL/min. **TENVIR EM** 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**]

Patients with Hepatic Impairment

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

INDICATIONS

TENVIR-EM 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.

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

- It is not recommended that **TENVIR EM** be used as a component of a triple nucleoside regimen.
- **TENVIR EM** should not be coadministered with lamivudine+tenofovir DF+Efavirenz, emtricitabine, tenofovir DF or lamivudine-containing products [see **WARNINGS AND PRECAUTIONS**].
- In treatment experienced patients, the use of **TENVIR EM** should be guided by laboratory testing and treatment history.

DOSAGE AND ADMINISTRATION

The dosage of **TENVIR-EM** is one tablet (containing 200 mg of emtricitabine and 300 mg of tenofovir DF) once daily taken orally with or without food.

Dose adjustment for renal impairment

Significantly increased drug exposures occurred when emtricitabine or tenofovir DF were administered to patients with moderate to severe renal impairment. Therefore, the dosing interval of **TENVIR-EM** should be adjusted in patients with baseline creatinine clearance of 30-49 mL/min using the recommendations in Table 2. The safety and effectiveness of these dosing interval adjustment recommendations have not been clinically evaluated; therefore, clinical response to treatment and renal function should be closely monitored in these patients.

No dose adjustment is necessary for patients with mild renal impairment (creatinine clearance of 50–80 mL/min). Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients with mild renal impairment [see **WARNINGS AND PRECAUTIONS**].

Table 2: Dosage Adjustment for Patients with Altered Creatinine Clearance

	Creatinine Clearance (mL/min)^a		
	≥ 50	30-49	<30 (including patients requiring hemodialysis)
Recommended Dosing Interval	Every 24 hours	Every 48 hours	TENVIR-EM should not be administered

^a Calculated using ideal (lean) body weight

Special Population

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of emtricitabine or tenofovir DF did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. In general, dose selection for elderly patients should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with **TENVIR-EM** should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Patients co-infected with HIV and HBV

It is recommended that all patients with HIV-1 be tested for the presence of chronic HBV before initiating antiretroviral therapy. **TENVIR-EM** is not indicated for the treatment of chronic HBV infection and the safety and efficacy of emtricitabine and tenofovir DF have not been established in patients co-infected with HBV and HIV. Severe acute exacerbations of hepatitis B have been reported in patients after the discontinuation of emtricitabine and tenofovir DF. Hepatic function should be closely monitored with both clinical and laboratory follow up for at least several months in patients who discontinue **TENVIR-EM** and are co-infected with HIV and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

New Onset or Worsening of Renal Impairment

Emtricitabine and tenofovir are principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir DF [see **UNDESIRABLE EFFECTS**].

It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with **TENVIR-EM**. Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment, including patients who have previously experienced renal events while receiving adefovir dipivoxil.

Dosing interval adjustment of **TENVIR-EM** and close monitoring of renal function are recommended in all patients with creatinine clearance 30-49 mL/min. No safety or efficacy data are available in patients with renal impairment who received tenofovir DF and emtricitabine using these dosing guidelines, so the potential benefit of tenofovir/emtricitabine therapy should be assessed against the potential risk of renal toxicity. **TENVIR-EM** should not be administered to patients with creatine clearance <30 mL/min or patients requiring hemodialysis.

TENVIR-EM should be avoided with concurrent or recent use of a nephrotoxic agent.

Coadministration with Other Products

TENVIR EM is a fixed-dose combination of emtricitabine and tenofovir disoproxil fumarate. **TENVIR EM** should not be coadministered with tenofovir DF + lamivudine + efavirenz, emtricitabine, or tenofovir DF. Due to similarities between emtricitabine and lamivudine, **TENVIR EM** should not be coadministered with other drugs containing lamivudine, including lamivudine/zidovudine, Lamivudine or lamivudine-HBV (lamivudine), abacavir sulfate/lamivudine, or abacavir sulfate/lamivudine/zidovudine.

TENVIR EM should not be administered with adefovir dipivoxil.

Decreases in Bone Mineral Density

Bone mineral density (BMD) monitoring should be considered for HIV-1 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.

Tenofovir DF: In a 144-week study of treatment naïve patients, decreases in bone mineral density were seen at the lumbar spine and hip in both arms of the study. At Week 144, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in patients receiving tenofovir DF + lamivudine + efavirenz compared with patients receiving stavudine + lamivudine + efavirenz. Changes in BMD at the hip were similar between the two treatment groups. In both groups, the majority of the reduction in BMD occurred in the first 24–48 weeks of the study and this reduction was sustained through 144 weeks. Altogether 28% of tenofovir DF -treated patients versus 21% of the comparator 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 tenofovir DF group and 6 patients in the comparator group. Tenofovir DF was associated with significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide, and urinary N-telopeptide), suggesting increased bone turnover. Serum parathyroid hormone levels and 1, 25 Vitamin D levels were also higher in patients receiving tenofovir DF. The effects of tenofovir DF 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 which may contribute to fractures) have been reported in association with the use of tenofovir DF [see **UNDESIRABLE EFFECTS**].

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement and

“cushingoid appearance” have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Immune Reconstitution Syndrome

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

Early Virologic Failure

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 substitutions have been reported. Triple nucleoside regimens should therefore be used with caution. Patients on a therapy utilizing a triple nucleoside-only regimen should be carefully monitored and considered for treatment modification.

Drug Interactions

No drug interaction studies have been conducted using **TENVIR-EM**. Drug interaction studies have been conducted with emtricitabine and tenofovir disoproxil fumarate, the components of **TENVIR-EM**. This section describes clinically relevant drug interactions observed with emtricitabine and tenofovir disoproxil fumarate.

Didanosine

Coadministration of **TENVIR-EM** and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine associated adverse reactions. Didanosine should be discontinued in patients who develop didanosine-associated adverse reactions.

When tenofovir disoproxil fumarate was administered with didanosine the C_{max} and AUC of didanosine administered as either the buffered or enteric-coated formulation increased significantly. The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine associated adverse reactions, including pancreatitis, and neuropathy. Suppression of CD4⁺ cell counts has been observed in patients receiving tenofovir DF with didanosine 400 mg daily.

In adults weighing >60 kg, the didanosine dose should be reduced to 250 mg when it is coadministered with **TENVIR-EM**. Data are not available to recommend a dose adjustment of didanosine for patients weighing >60 kg. When coadministered, **TENVIR-EM** and didanosine EC may be taken under fasted conditions or with a light meal (<400

kcal, 20% fat). Coadministration of didanosine buffered tablet formulation with **TENVIR-EM** should be under fasted conditions.

Atazanavir

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

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

Lopinavir/Ritonavir

Lopinavir/ritonavir has been shown to increase tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving lopinavir/ritonavir and **TENVIR-EM** should be monitored for **TENVIR-EM**-associated adverse reactions. **TENVIR-EM** should be discontinued in patients who develop **TENVIR-EM**-associated adverse reactions.

Drugs affecting Renal function

Emtricitabine and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. No drug-drug interactions due to competition for renal excretion have been observed; however, coadministration of **TENVIR-EM** with drugs that are eliminated by active tubular secretion may increase concentrations of emtricitabine, tenofovir, and/or the coadministered drug. Some examples include, but are not limited to acyclovir, adefovir dipivoxil, cidofovir, ganciclovir, valacyclovir, and valganciclovir. Drugs that decrease renal function may increase concentrations of emtricitabine and/or tenofovir.

Patients with Renal Impairment

It is recommended that the dosing interval for **TENVIR-EM** be modified in patients with creatinine clearance 30–49 mL/min. **TENVIR-EM** 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**].

Pregnancy

Pregnancy Category B:

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

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

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

Lactation

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

Pediatric Use

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

Geriatric Use

Clinical studies of emtricitabine or tenofovir DF did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly patients should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

UNDESIRABLE EFFECTS

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

- Lactic Acidosis/Severe Hepatomegaly with Steatosis (See **BOXED WARNING, WARNINGS AND PRECAUTIONS**)
- Severe Acute Exacerbations of hepatitis B (See **BOXED WARNING, WARNINGS AND PRECAUTIONS**)
- New Onset or Worsening Renal Impairment (See **WARNINGS AND PRECAUTIONS**)
- Decreases in Bone Mineral Density (See **WARNINGS AND PRECAUTIONS**)
- Immune Reconstitution Syndrome (See **WARNINGS AND PRECAUTIONS**)

Adverse Reactions from Clinical Trials Experience

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

The most common adverse reactions (incidence $\geq 10\%$, any severity) occurring in Study 934, an active-controlled clinical study of efavirenz, emtricitabine, and tenofovir disoproxil fumarate, include diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash. See also Table 3 for the frequency of treatment-emergent adverse reactions (Grade 2–4) occurring in $\geq 5\%$ of patients treated with efavirenz, emtricitabine, and tenofovir disoproxil fumarate in this study.

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

Study 934 - Treatment Emergent Adverse Reactions: In Study 934, 511 antiretroviral-naïve patients received either tenofovir DF + emtricitabine administered in combination with efavirenz (n=257) or zidovudine/lamivudine administered in combination with efavirenz (n=254). Adverse reactions observed in this study were generally consistent with those seen in other studies in treatment-experienced or treatment-naïve patients receiving tenofovir DF and/or emtricitabine (Table 3).

Table 3: Selected Treatment-Emergent Adverse Reactions^a (Grades 2–4) Reported in $\geq 5\%$ in Any Treatment Group in Study 934 (0–144 Weeks)

	FTC + TDF + EFV^b	AZT/3TC + EFV
	N=257	N=254
Gastrointestinal Disorder		
Diarrhea	9%	5%
Nausea	9%	7%
Vomiting	2%	5%
General Disorders and Administration Site Condition		
Fatigue	9	8
Infections and Infestations		
Sinusitis	8	4
Upper respiratory tract infections	8	5

Nasopharyngitis	5	3
Nervous System Disorders		
Headache	6	5
Dizziness	8	7
Psychiatric Disorders		
Depression	9	7
Insomnia	5	7
Skin and Subcutaneous Tissue Disorders		
Rash event ^c	7	9

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

^b. From Weeks 96 to 144 of the study, patients received tenofovir DF + emtricitabine with efavirenz in place of Tenofovir DF + Emtricitabine with efavirenz.

^c. Rash event includes rash, exfoliative rash, rash generalized, rash macular, rash maculo-papular, rash pruritic, and rash vesicular.

Laboratory Abnormalities:

Laboratory abnormalities observed in this study were generally consistent with those seen in other studies of tenofovir DF and/or emtricitabine (Table 4).

Table 4: Significant Laboratory Abnormalities Reported in ≥1% of Patients in Any Treatment Group in Study 934 (0–144 Weeks)

	FTC + TDF + EFV ^b	AZT/3TC + EFV
	N=257	N=254
Any ≥ Grade 3 Laboratory Abnormality	30%	26%
Fasting Cholesterol (>240mg/dL)	22%	24%
Creatinine Kinase		
(M:>990 U/L)	9%	7%
(F:>845 U/L)		
Serum Amylase (>175 U/L)	8%	4%
Alkaline Phosphatase (>550 U/L)	1%	0%
AST		
(M:>180 U/L)	3%	3%
(F:>170 U/L)		

ALT (M:>215 U/L) (F:>170 U/L)	2%	3%
Hemoglobin (<8.0 mg/dL)	0%	4%
Hyperglycemia (>250 mg/dL)	2%	1%
Hematuria (>75 RBC/HPF)	3%	2%
Glycemia ($\geq 3+$)	<1%	1%
Neutrophils (<750/mm ³)	3%	5%
Fasting Triglycerides (>750 mg/dL)	4%	2%

- ^a From Weeks 96 to 144 of the study, patients received tenofovir DF + emtricitabine with efavirenz in place of Tenofovir DF + Emtricitabine with efavirenz.

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

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

Observed During Clinical Practice:

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

Immune system disorders: Allergic reaction, including angioedema

Metabolism and nutrition disorders: Hypophosphatemia, hypokalemia lactic acidosis,

Respiratory, thoracic, and mediastinal disorders: dyspnea

Gastrointestinal disorders: Abdominal pain, pancreatitis, increased amylase

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

Skin and Subcutaneous Tissue Disorders :rash

Musculoskeletal and Connective Tissue Disorders: rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy

Renal and urinary disorders: Renal impairment, renal failure, fanconi syndrome, proximal tubulopathy, proteinuria, increased creatinine, acute tubular necrosis, interstitial nephritis (including acute cases)nephrogenic diabetes insipidus,renal insufficiency polyuria.

OVERDOSAGE

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

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

Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of tenofovir DF, a 4-hour haemodialysis session removed approximately 10% of the administered tenofovir dose.

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

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

PACKAGING INFORMATION

TENVIR-EM tabletsContainer of 30 tablets

Last updated: January 2010