

Tenofovir disoproxil fumarate tablets

TENVIR

WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS AND POST TREATMENT EXACERBATION OF HEPATITIS.

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

SEVERE ACUTE EXACERBATIONS OF HEPATITIS HAVE BEEN REPORTED IN HBV-INFECTED PATIENTS WHO HAVE DISCONTINUED ANTI-HEPATITIS B THERAPY INCLUDING TENOFOVIR DISOPROXIL FUMARATE. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE ANTI-HEPATITIS B THERAPY, INCLUDING TENOFOVIR. IF APPROPRIATE, RESUMPTION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS AND PRECAUTIONS).

COMPOSITION

Each film-coated tablet contains

Tenofovir disoproxil fumarate 300mg

Equivalent to Tenofovir disoproxil245mg

DOSAGE FORM

Oral, film-coated tablet

PHARMACOLOGY

Pharmacodynamics

Tenofovir disoproxil fumarate is an antiviral drug. 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, an obligate chain terminator. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase and HBV 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 alpha and beta, and mitochondrial DNA polymerase gamma.

Pharmacokinetics

The pharmacokinetics of tenofovir disoproxil fumarate has been evaluated in healthy volunteers and HIV-1 infected individuals. Tenofovir pharmacokinetics is similar between these populations.

Absorption: Tenofovir disoproxil fumarate is a water-soluble diester prodrug of the active ingredient tenofovir. The oral bioavailability of tenofovir from tenofovir disoproxil fumarate in fasted patients is approximately 25%. Following oral administration of a single dose of tenofovir disoproxil fumarate 300 mg to HIV-1 infected patients in the fasted state, maximum serum concentrations (C_{max}) are achieved in 1.0 ± 0.4 hrs. C_{max} and AUC values are 0.30 ± 0.09 ng/mL and 2.29 ± 0.69 ng·hr/mL, respectively.

The pharmacokinetics of tenofovir are dose proportional over a tenofovir disoproxil fumarate dose range of 75 to 600 mg and are not affected by repeated dosing.

Effects of Food on Oral Absorption: Administration of tenofovir following a high-fat meal (~700 to 1000 kcal containing 40 to 50% fat) increases the oral bioavailability, with an increase in tenofovir AUC_{0-∞} of approximately 40% and an increase in C_{max} of approximately 14%. However, administration of tenofovir with a light meal did not have a significant effect on the pharmacokinetics of tenofovir when compared to fasted administration of the drug. Food delays the time to tenofovir C_{max} by approximately 1 hour. C_{max} and AUC of tenofovir are 0.33 ± 0.12 µg/mL and 3.32 ± 1.37 µg·hr/mL following multiple doses of tenofovir 300 mg once daily in the fed state, when meal content was not controlled.

Distribution: In vitro binding of tenofovir to human plasma or serum proteins is less than 0.7 and 7.2%, respectively, over the tenofovir concentration range 0.01 to 25 µg/mL. The volume of distribution at steady state is 1.3 ± 0.6 L/kg and 1.2 ± 0.4 L/kg, following intravenous administration of tenofovir 1.0 mg/kg and 3.0 mg/kg

Metabolism and Elimination: In vitro studies indicate that neither tenofovir disoproxil nor tenofovir are substrates of CYP450 enzymes.

Following IV administration of tenofovir, approximately 70-80% of the dose is recovered in the urine as unchanged tenofovir within 72 hours of dosing. Following single dose, oral administration of tenofovir disoproxil fumarate, the terminal elimination half-life of tenofovir is approximately 17 hours. After multiple oral doses of tenofovir disoproxil fumarate 300 mg once daily (under fed conditions), $32 \pm 10\%$ of the administered dose is recovered in urine over 24 hours. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. There may be competition for elimination with other compounds that are also renally eliminated.

Special Populations

Race: There were insufficient numbers from racial and ethnic groups other than Caucasian to adequately determine potential pharmacokinetic differences among these populations.

Gender: Tenofovir pharmacokinetics are similar in male and female patients.

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

Pharmacokinetic studies have not been performed in pediatric subjects <12 years of age.

Geriatric Patients: Pharmacokinetic studies have not been performed in the elderly (>65 years).

Patients with Impaired Renal Function: The pharmacokinetics of tenofovir are altered in patients with renal impairment [see **WARNINGS AND PRECAUTIONS**]. In patients with creatinine clearance <50 mL/min or with end-stage renal disease (ESRD) requiring dialysis, C_{\max} , and $AUC_{0-\infty}$ of tenofovir were increased (Table 1). It is recommended that the dosing interval for **TENVIR** be modified in patients with creatinine clearance <50 mL/min or in patients with ESRD who require dialysis [see **DOSAGE AND ADMINISTRATION**].

Table 1. Pharmacokinetic Parameters (Mean \pm SD) of Tenofovir^a in Patients with Varying Degrees of Renal Function

Baseline Creatinine Clearance (mL/min)	>80 (N=3)	50–80 (N=10)	30–49 (N=8)	12–29 (N=11)
C_{\max} ($\mu\text{g/mL}$)	0.34 ± 0.03	0.33 ± 0.06	0.37 ± 0.16	0.60 ± 0.19
$AUC_{0-\infty}$ ($\mu\text{g}\cdot\text{hr/mL}$)	2.18 ± 0.26	3.06 ± 0.93	6.01 ± 2.50	15.98 ± 7.22
CL/F (mL/min)	1043.7 ± 115.4	807.7 ± 279.2	444.4 ± 209.8	177.0 ± 97.1
CL _{renal} (mL/min)	243.5 ± 33.3	168.6 ± 27.5	100.6 ± 27.5	43.0 ± 31.2

^a: 300 mg, single dose of tenofovir disoproxil fumarate

Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of tenofovir disoproxil fumarate,

a four-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

Patients with Hepatic Impairment: The pharmacokinetics of tenofovir following a 300 mg single dose of tenofovir disoproxil fumarate 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. No change in **TENVIR** dosing is required in patients with hepatic impairment.

INDICATIONS

HIV infection

TENVIR tablets are indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older.

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

TENVIR should not be used in combination with tenofovir/emtricitabine or efavirenz/emtricitabine/tenofovir disoproxil fumarate [see **WARNINGS AND PRECAUTIONS**].

Chronic Hepatitis B

TENVIR is indicated for the treatment of chronic hepatitis B in adults.

The following points should be considered when initiating therapy with tenofovir disoproxil fumarate for the treatment of HBV infection:

- This indication is based primarily on data from treatment of subjects who were nucleoside-treatment-naïve and a smaller number of subjects who had previously received lamivudine or adefovir dipivoxil. Subjects were adults with HBeAg positive and HBeAg-negative chronic hepatitis B with compensated liver disease.
- Tenofovir was evaluated in a limited number of subjects with chronic hepatitis B and decompensated liver disease [See **UNDESIRABLE EFFECTS**].
- The numbers of subjects in clinical trials who had lamivudine- or adefovir associated substitutions at baseline were too small to reach conclusions of efficacy.

DOSAGE AND ADMINISTRATION

Recommended Dose

For treatment of HIV-1 and chronic hepatitis B:

The dose of **TENVIR** is 300 mg once daily taken orally, without regard to food.

In the treatment of chronic hepatitis B, the optimal duration of treatment is unknown.

Recommended Dose in Pediatric Patients (≥12 Years of Age and ≥35 kg) for treatment of HIV-1

For the treatment of HIV-1 in pediatric patients 12 years of age and older with body weight ≥ 35 kg (≥ 77 lb): The dose is one 300 mg tenofovir tablet once daily taken orally, without regard to food.

Dose Adjustment for Renal Impairment

Significantly increased drug exposures occurred when tenofovir disoproxil fumarate was administered to patients with moderate to severe renal impairment. Therefore, the dosing interval of tenofovir disoproxil fumarate should be adjusted in patients with baseline creatinine clearance < 50 mL/min using the recommendations in Table 2. These dosing interval recommendations are based on modeling of single-dose pharmacokinetic data in non-HIV and non-HBV 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; therefore, clinical response to treatment and renal function should be closely monitored in these patients. [See **WARNINGS AND PRECAUTIONS**]

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

Table 2. Dosage Adjustment for Patients with Altered Creatinine Clearance

	Creatinine Clearance (mL/min) ^a			Hemodialysis Patients
	≥ 50	30-49	10-29	
Recommended 300 mg Dosing Interval	Every 24 hours	Every 48 hours	Twice a week	Every 7 days or after a total of approximately 12 hours of dialysis ^b
^a : Calculated using ideal (lean) body weight.				
^b : Generally once weekly assuming three hemodialysis sessions a week of approximately 4 hours duration. Tenofovir disoproxil fumarate should be administered following completion of dialysis.				

The pharmacokinetics of tenofovir have not been evaluated in non-hemodialysis patients with creatinine clearance < 10 mL/min; therefore, no dosing recommendation is available for these patients.

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

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 including tenofovir 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** 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).

Exacerbation of Hepatitis after Discontinuation of Treatment

Discontinuation of anti-HBV therapy, including tenofovir, may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue **TENVIR** should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted.

New Onset or Worsening Renal Impairment

Tenofovir is 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 disoproxil fumarate (see **UNDESIRABLE EFFECTS, POST MARKETING EXPERIENCE**).

It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with **TENVIR**. 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** and close monitoring of renal function are recommended in all patients with creatinine clearance <50 mL/min (see **DOSAGE AND ADMINISTRATION**). No safety or efficacy data are available in patients with renal impairment who received tenofovir disoproxil fumarate using these dosing guidelines, so the potential benefit of **TENVIR** therapy should be assessed against the potential risk of renal toxicity.

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

Patients Co-infected with HIV-1 and HBV

Due to the risk of development of HIV-1 resistance, **TENVIR** should only be used in HIV-1 and HBV coinfecting patients as part of an appropriate antiretroviral combination regimen. HIV-1 antibody testing should be offered to all HBV-infected

patients before initiating therapy with **TENVIR**. It is also recommended that all patients with HIV-1 be tested for the presence of chronic hepatitis B before initiating treatment with **TENVIR**.

Co administration with other products

TENVIR should not be used in combination with the fixed-dose combination products tenofovir disoproxil fumarate/emtricitabine or efavirenz/emtricitabine/tenofovir disoproxil fumarate, since tenofovir disoproxil fumarate is a component of these products. **TENVIR** should not be administered in combination with adefovir dipivoxil [see **WARNINGS AND PRECAUTIONS: Drug interactions**].

Decreases in Bone Mineral Density

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

In HIV-infected patients treated with tenofovir 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 study. At Week 144, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in patients receiving tenofovir disoproxil fumarate + lamivudine + efavirenz (-2.2% ± 3.9) compared with patients receiving stavudine + lamivudine + efavirenz (-1.0% ± 4.6). Changes in BMD at the hip were similar between the two treatment groups (-2.8% ± 3.5 in the tenofovir disoproxil fumarate group vs. -2.4% ± 4.5 in the stavudine group). In both groups, the majority of the reduction in BMD occurred in the first 24–48 weeks of the study and this reduction was sustained through Week 144. Twenty-eight percent of tenofovir disoproxil fumarate-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 tenofovir disoproxil fumarate 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 tenofovir disoproxil fumarate 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 tenofovir disoproxil fumarate group. Except for bone specific alkaline phosphatase, these changes resulted in values that remained within the normal range. The effects of tenofovir disoproxil fumarate 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) have been reported in association with the use of tenofovir disoproxil fumarate (see **UNDESIRABLE EFFECTS, POST MARKETING EXPERIENCE**)

The bone effects of tenofovir disoproxil fumarate have not been studied in patients with chronic HBV infection.

Fat Redistribution

In HIV-infected patients 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 tenofovir disoproxil fumarate. 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.

Pregnancy

Pregnancy category B: 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** should be used during pregnancy only if clearly needed.

Lactation

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV-1. Studies in rats have demonstrated that tenofovir is secreted in milk. It is not known whether tenofovir is excreted in human milk. 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.**

Pediatric Use

Pediatric Patients 12 Years of Age and Older

The safety of tenofovir in pediatric patients aged 12 to <18 years is supported by data from one randomized study in which tenofovir was administered to HIV-1 infected treatment-experienced subjects. In this study, the pharmacokinetic profile of tenofovir was similar to that found to be safe and effective in adult clinical trials.

In Study 321, 87 treatment-experienced subjects 12 to <18 years of age were treated with tenofovir (N=45) or placebo (N=42) in combination with an optimized background regimen (OBR) for 48 weeks. The mean baseline CD4 cell count was 374 cells/mm³ and the mean baseline plasma HIV-1 RNA was 4.6 log₁₀ copies/mL. At baseline, 90% of subjects harbored NRTI resistance-associated substitutions in their HIV-1 isolates. Overall, the trial failed to show a difference in virologic response between the tenofovir and placebo treatment groups. Subgroup analyses suggest the lack of difference in virologic response may be attributable to imbalances between treatment arms in baseline viral susceptibility to tenofovir and OBR.

Although changes in HIV-1 RNA in these highly treatment-experienced subjects were less than anticipated, the comparability of the pharmacokinetic and safety data to that observed in adults supports the use of tenofovir in pediatric patients ≥12 years of age who weigh ≥35 kg and whose HIV-1 isolate is expected to be sensitive to tenofovir. [See **WARNINGS AND PRECAUTIONS, UNDESIRABLE EFFECTS**].

Safety and effectiveness in pediatric patients less than 12 years of age have not been established

Geriatric Use

Clinical studies of tenofovir did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly 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.

Patients with Impaired Renal Function

It is recommended that the dosing interval for **TENVIR** be modified in patients with creatinine clearance <50 mL/min or in patients with ESRD who require dialysis [see **DOSAGE AND ADMINISTRATION, PHARMACOLOGY**]

DRUG INTERACTIONS

This section describes clinically relevant drug interactions with tenofovir disoproxil fumarate.

Didanosine

Coadministration of **TENVIR** 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 administered with tenofovir disoproxil fumarate, 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 disoproxil fumarate (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**. Data are not available to recommend a dose adjustment of didanosine for patients weighing <60 kg. When coadministered, **TENVIR** 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** should be under fasted conditions.

Atazanavir

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

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

Lopinavir/Ritonavir

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

Drugs Affecting Renal Function

Since tenofovir is primarily eliminated by the kidneys, coadministration of tenofovir disoproxil fumarate with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir and/or increase the concentrations of other renally eliminated drugs. Some examples include, but are not limited to, didanosine, acyclovir, valacyclovir, ganciclovir, and valganciclovir. Drugs that decrease renal function may also increase serum concentrations of tenofovir. In the

treatment of chronic hepatitis B, tenofovir should not be administered in combination with adefovir dipivoxil.

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 Exacerbation of Hepatitis [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 trial experience

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

Clinical Trials in Patients with HIV Infection

More than 12,000 patients have been treated with tenofovir disoproxil fumarate alone or in combination with other antiretroviral medicinal products for periods of 28 days to 215 weeks in clinical trials and expanded access studies. A total of 1,544 patients have received tenofovir disoproxil fumarate 300 mg once daily; over 11,000 patients have received tenofovir disoproxil fumarate in expanded access studies.

The most common adverse reactions (incidence $\geq 10\%$, Grades 2–4) identified from any of the 3 large controlled clinical trials include rash, diarrhea, headache, pain, depression, asthenia, and nausea.

Treatment-Naïve Patients

Study 903 Treatment-Emergent Adverse Events: The most common adverse reactions seen in a double-blind comparative controlled study in which 600 treatment-naïve patients received tenofovir disoproxil fumarate (N=299) or stavudine (N=301) in combination with lamivudine and efavirenz for 144 weeks (Study 903) were mild to moderate gastrointestinal events and dizziness.

Mild adverse events (Grade 1) were common with a similar incidence in both arms, and included dizziness, diarrhea and nausea. Selected treatment-emergent moderate to severe adverse events are summarized in Table 3.

Table 3: Selected Treatment-Emergent Adverse reactions ^a (grades 2-4) reported in $\geq 5\%$ in any treatment group in study

903 (0-144 weeks)		
	Tenofovir 3TC+EFV	DF+ d4T + 3TC + EFV
	N=299	N=301
Body as a Whole		
Headache	14%	17%
Pain	13%	12%
Fever	8%	7%
Abdominal Pain	7%	12%
Back Pain	9%	8%
Asthenia	6%	7%
Digestive System		
Diarrhea	11%	13%
Nausea	8%	9%
Dyspepsia	4%	5%
Vomiting	5%	9%
Metabolic disorders		
Lipodystrophy ^b	1%	8%
Musculoskeletal		
Arthralgia	5%	7%
Myalgia	3%	5%
Nervous System		
Depression	11%	10%
Insomnia	5%	8%
Dizziness	3%	6%
Anxiety	6%	6%
Peripheral neuropathy ^c	1%	5%
Respiratory		
Pneumonia	5%	5%
Skin and Appendages		
Rash Event ^d	18%	12%
<p>^{a.} Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.</p> <p>^{b.} Lipodystrophy represents a variety of investigator-described adverse events not a protocol-defined syndrome</p> <p>^{c.} Peripheral neuropathy includes peripheral neuritis and neuropathy.</p>		

^d. Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash.

Laboratory Abnormalities: With the exception of fasting cholesterol and triglyceride elevations that were more common in the stavudine group (40% and 9%) compared with tenofovir disoproxil fumarate (19% and 1%), laboratory abnormalities observed in this study occurred with similar frequency in the tenofovir disoproxil fumarate and stavudine treatment arms. A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 4.

Table 4: Grade 3 / 4 Laboratory Abnormalities reported in ≥ 1% of tenofovir DF-treated patients in study 903 (0-144 weeks)		
	Tenofovir DF + 3TC + EFV	d4T + 3TC + EFV
	N=299	N=301
Any ≥ Grade 3 Laboratory Abnormality	36%	42%
Fasting cholesterol (>240 mg/dL)	19%	40%
Creatine Kinase (M: >990 U/L) (F: >845 U/L)	12%	12%
Serum Amylase (>175 U/L)	9%	8%
AST (M: >180 U/L) (F: >170 U/L)	5%	7%
ALT (M: >215 U/L) (F: >170 U/L)	4%	5%
Hematuria (>100 RBC/HPF)	7%	7%
Neutrophil (<750/mm ³)	3%	1%
Fasting Triglyceride (>750 mg/dL)	1%	9%

Study 934 - Treatment Emergent Adverse Reactions: In Study 934, 511 antiretroviral naïve patients received either tenofovir disoproxil fumarate + 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 previous studies in treatment-experienced or treatment-naïve patients (Table 5).

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

	TDF^b + FTC + EFV	AZT/3TC + EFV
	N=257	N=254

Gastrointestinal Disorder		
Diarrhea	9%	5%
Nausea	9%	7%
Vomiting	2%	5%
General Disorders and Administration Site Condition		
Fatigue	9%	8%
Infections and Infestations		
Sinusitis	8%	4%
Upper respiratory tract infections	8%	5%
Nasopharyngitis	5%	3%
Nervous System Disorders		
Headache	6%	5%
Dizziness	8%	7%
Psychiatric Disorders		
Depression	9%	7%
Insomnia	5%	7%
Skin and Subcutaneous Tissue Disorders		
Rash event ^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 (TDF)/emtricitabine with efavirenz in place of TDF /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 previous studies (Table 6).

TABLE 6. Significant Laboratory Abnormalities Reported in ≥1% of Patients in Any Treatment Group in Study 934 (0–144 Weeks)

	TDF^a+ FTC + EFV	AZT/3TC + EFV
	N=257	N=254
Any ≥ Grade 3 Laboratory Abnormality	30%	26%
Fasting Cholesterol (>240 mg/dL)	22%	24%

Creatine Kinase (M: >990 U/L) (F: >845 U/L)	9%	7%
Serum Amylase (>175 U/L)	8%	4%
Alkaline Phosphatase (>550 U/L)	1%	0%
AST (M: >180 U/L) (F: >170 U/L)	3%	3%
ALT (M: >215 U/L) (F: >170 U/L)	2%	3%
Hemoglobin (<8.0 mg/dL)	0%	4%
Hyperglycemia (>250 mg/dL)	2%	1%
Hematuria (>75 RBC/HPF)	3%	2%
Glycosuria (≥3+)	<1%	1%
Neutrophils (<750/mm ³)	3%	5%
Fasting Triglycerides (>750 mg/dL)	4%	2%

^a: From Weeks 96 to 144 of the study, patients received TDF/emtricitabine with efavirenz in place of TDF + emtricitabine with efavirenz.

Treatment-Experienced Patients

Treatment-Emergent Adverse Events: The adverse reactions seen in treatment experienced patients were generally consistent with those seen in treatment naïve patients including mild to moderate gastrointestinal events, such as nausea, diarrhea, vomiting and flatulence. Less than 1% of patients discontinued participation in the clinical studies due to gastrointestinal adverse events (Study 907).

A summary of moderate to severe, treatment-emergent adverse events that occurred during the first 48 weeks of Study 907 is provided in Table 7.

Table 7: Selected treatment-emergent adverse reactions ^a(grades 2-4) reported in ≥3% in any treatment group in study 907 (0-48 weeks)				
	Tenofovir DF (N=368) (week 0-24)	Placebo (N=182) (week 0-24)	Tenofovir DF (N=368) (week 0-48)	Placebo crossover to tenofovir DF (N=170) (week 24-48)
Body as a whole				
Asthenia	7%	6%	11%	1%

Pain	7%	7%	12%	4%
Headache	5%	5%	8%	2%
Abdominal Pain	4%	3%	7%	6%
Back Pain	3%	3%	4%	2%
Chest Pain	3%	1%	3%	2%
Fever	2%	2%	4%	2%
Digestive System				
Diarrhea	11%	10%	16%	11%
Nausea	8%	5%	11%	7%
Vomiting	4%	1%	7%	5%
Anorexia	3%	2%	4%	1%
Dyspepsia	3%	2%	4%	2%
Flatulence	3%	1%	4%	1%
Respiratory				
Pneumonia	2%	0%	3%	2%
Nervous System				
Depression	4%	3%	8%	4%
Insomnia	3%	2%	4%	4%
Peripheral Neuropathy ^b	3%	3%	5%	2%
Dizziness	1%	3%	3%	1%
Skin and Appendage				
Rash Event ^c	5%	4%	7%	1%
Sweating	3%	2%	3%	1%
Musculoskeletal				
Myalgia	3%	3%	4%	1%
Metabolic				
Weight Loss	2%	1%	4%	2%
<p>a. Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug</p> <p>b. Peripheral neuropathy includes peripheral neuritis and neuropathy</p> <p>c. Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash.</p>				

Laboratory Abnormalities: Laboratory abnormalities observed in this study occurred with similar frequency in the tenofovir DF and placebo-treated groups. A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 8 below.

Table 8: Grade 3/4 Laboratory Abnormalities Reported in ≥1% of tenofovir DF-Treated Patients in Study 907 (0–144 weeks)				
	Tenofovir DF (N=368) (Week 0–24)	Placebo (N=182) (Week 0–24)	Tenofovir DF (N=368) (Week 0–48)	Placebo Crossover to tenofovir DF (N=170) (Week 24–48)
	%	%	%	%
Any ≥ Grade 3 Laboratory Abnormality	25%	38%	35%	34%
Triglycerides (>750 mg/dL)	8%	13%	11%	9%
Creatine Kinase (M: >990 U/L) (F: >845 U/L)	7%	14%	12%	12%
Serum Amylase (>175 U/L)	6%	7%	7%	6%
Glucosuria (≥3+)	3%	3%	3%	2%
AST (M: >180 U/L) (F: >170 U/L)	3%	3%	4%	5%
ALT (M: >215 U/L) (F: >170 U/L)	2%	2%	4%	5%
Serum Glucose (>250 U/L)	2%	4%	3%	3%
Neutrophils (<750 mm ³)	1%	1%	2%	1%

Clinical Trials in Pediatric Subjects 12 Years of Age and Older with HIV-1 Infection

Assessment of adverse reactions is based on one randomized trial (Study 321) in 87 HIV-1 infected pediatric subjects (12 to <18 years of age) who received treatment with tenofovir (N=45) or placebo (N=42) in combination with other antiretroviral

agents for 48 weeks. The adverse reactions observed in subjects who received treatment with tenofovir were consistent with those observed in clinical trials in adults. Bone effects observed in pediatric subjects 12 years of age and older were consistent with those observed in adult clinical trials [See **Warnings and Precautions**].

Clinical Trials in Patients with Chronic Hepatitis B

Clinical Trials in Adult Subjects with Chronic Hepatitis B and Compensated Liver Disease

Treatment-Emergent Adverse Reactions: In controlled clinical trials in subjects with chronic hepatitis B (0102 and 0103), more subjects treated with tenofovir during the 48 week double-blind period experienced nausea: 9% with tenofovir versus 2% with adefovir dipivoxil. Other treatment-emergent adverse reactions reported in >5% of subjects treated with tenofovir included: abdominal pain, diarrhea, headache, dizziness, fatigue, nasopharyngitis, back pain and skin rash.

No significant change in the tolerability profile (nature or severity of adverse reactions) was observed in subjects continuing treatment with tenofovir for up to 144 weeks in these studies.

Laboratory Abnormalities: A summary of Grade 3 and 4 laboratory abnormalities through Week 48 is provided in Table 9. Grade 3/4 laboratory abnormalities were similar in subjects continuing tenofovir treatment for up to 144 weeks in these studies.

Table 9: Grade 3/4 Laboratory Abnormalities Reported in ≥1% of Tenofovir diphoproxil fumarate-Treated Patients in Studies 0102 and 0103 (0-48 Weeks)

	Tenofovir disoproxil fumarate (N=426)	Adefovir dipivoxil (N=215)
Any ≥ Grade 3 Laboratory Abnormality	19%	13%
Creatine Kinase (M: >990U/L) (F: >845 U/L)	2%	3%
Serum Amylase (>175 U/L)	4%	1%
Glycosuria (≥3+)	3%	<1%
AST (M: >180 U/L) (F: >170 U/L)	4%	4%
ALT (M: >215 U/L) (F: >170 U/L)	10%	6%

The overall incidence of on-treatment ALT elevations (defined as serum ALT $>2 \times$ baseline and $>10 \times$ ULN, with or without associated symptoms) was similar between tenofovir disoproxil fumarate (2.6%) and adefovir dipivoxil (2%). ALT elevations generally occurred within the first 4–8 weeks of treatment and were accompanied by decreases in HBV DNA levels. No patient had evidence of decompensation. ALT flares typically resolved within 4 to 8 weeks without changes in study medication.

Clinical Trial in Adult Subjects with Chronic Hepatitis B and Decompensated Liver Disease

In a small randomized, double-blind, active-controlled trial (0108), subjects with CHB and decompensated liver disease received treatment with tenofovir or other antiviral drugs for up to 48 weeks. Among the 45 subjects receiving tenofovir, the most frequently reported treatment-emergent adverse reactions of any severity were abdominal pain (22%), nausea (20%), insomnia (18%), pruritus (16%), vomiting (13%), dizziness (13%), and pyrexia (11%). Two of 45 (4%) subjects died through Week 48 of the study due to progression of liver disease. Three of 45 (7%) subjects discontinued treatment due to an adverse event. Four of 45 (9%) subjects experienced a confirmed increase in serum creatinine of 0.5 mg/dL (1 subject also had a confirmed serum phosphorus < 2 mg/dL through Week 48). Three of these subjects (each of whom had a Child-Pugh score ≥ 10 and MELD score ≥ 14 at entry) developed renal failure. Because both tenofovir and decompensated liver disease may have an impact on renal function, the contribution of tenofovir to renal impairment in this population is difficult to ascertain. One of 45 subjects experienced an on-treatment hepatic flare during the 48 Week study.

Post marketing Experience: The following adverse reactions have been identified during postapproval use of tenofovir disoproxil fumarate. 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: Hypophosphataemia, hypokalemia, lactic acidosis.

Respiratory, Thoracic, and Mediastinal Disorders: Dyspnoea

Gastrointestinal Disorders: Abdominal pain, increased amylase, Pancreatitis

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

Skin and subcutaneous tissue disorders: Rash

Musculoskeletal and connective tissue disorders: rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy.

Renal and Urinary Disorders: acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, Proximal tubulopathy, Proteinuria, Increased creatinine, Acute tubular necrosis, Nephrogenic diabetes insipidus, Polyuria, Interstitial nephritis (including acute cases).

General disorders and administration site conditions: Asthenia

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

OVERDOSAGE

Limited clinical experience at doses higher than the therapeutic dose of tenofovir disoproxil fumarate 300 mg is available. In Study 901, 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.

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

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

SHELF-LIFE

24 months

STORAGE AND HANDLING INSTRUCTIONS

Store below 30°C

PACKAGING INFORMATION

TENVIR Tablets.....Container pack of 30 tablets

Last updated: October 2010