For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

Tenofovir Disoproxil Fumarate Tablets 300 mg

Tenvor

WARNING

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

TENVOR IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION AND THE SAFETY AND EFFICACY OF TENOFOVIR 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 TENOFOVIR. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE TENOFOVIR AND ARE CO-INFECTED WITH HBV AND HIV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS AND PRECAUTIONS).

Composition

Each film-coated tablet contains
Tenofovir Disoproxil Fumarate ..... 300 mg
equivalent to Tenofovir Disoproxil ..... 245 mg

Colours: Lake Indigo carmine and Titanium dioxide

Dosage form

Oral, film-coated tablets

Indications

Tenvor is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.

Dose and method of administration

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

Use in special populations

Paediatric Use

Safety and effectiveness in paediatric patients 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.

Dose Adjustment for Renal Impairment

Significantly increased drug exposures occurred when tenofovir was administered to patients with moderate to severe renal impairment. The dosing interval of **Tenvor** should be adjusted in patients with baseline creatinine clearance <50 mL/min using the recommendations in Table 1. The safety and effectiveness of these dosing interval adjustment recommendations have not been clinically evaluated, therefore, clinical response to treatment and renal function should be closely monitored in these patients.

Table 1: Dosage Adjustment for Patients with Altered Creatinine Clearance

	Creatinine Clearance (mL/min) [1]			Haemodialysis 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[2]

1.Calculated using ideal (lean) body weight.
2.Generally once weekly assuming three haemodialysis sessions a week of approximately 4 hours duration. **Tenvor** should be administered following completion of dialysis.

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

Contraindications

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

Warnings

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with **Tenvor** 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 Hepatitis B Virus

It is recommended that all patients with HIV be tested for the presence of chronic hepatitis B virus (HBV) before initiating antiretroviral therapy. **Tenvor** is not indicated for the treatment of chronic HBV infection and the safety and efficacy of tenofovir 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 tenofovir. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue tenofovir and are co-infected with HIV and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

Renal Impairment

Tenofovir is principally eliminated by the kidney. Dosing interval adjustment is recommended in all patients with creatinine clearance <50 mL/min (see Dosage and Administration). No safety data are available in patients with renal dysfunction who received tenofovir using these dosing guidelines.

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

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

Precautions

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 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 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 tenofovir disoproxil fumarate -associated changes in BMD and biochemical markers on long-term bone

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

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Immune Reconstitution Syndrome

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

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 foetus due to tenofovir. There are, however, no adequate and well-controlled studies in pregnant women. **Tenvor** should be used during pregnancy only if the potential benefit outweighs the potential risk.

Lactation

It is recommended that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. It is not know 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 **Tenvor**.

Drug Interactions

When administered with tenofovir, C_{max} and AUC of didanosine administered as either the buffered or enteric-coated formulation increased significantly (see Table 2). The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse events, including pancreatitis and neuropathy. In adults weighing >60kg, the didanosine dose should be reduced to 250 mg when it is co-administered with tenofovir. Data are not available to recommend a dose adjustment of didanosine for patients weighing <60 kg. When co-administered, tenofovir and didanosine EC may be taken under fasted conditions or with a light meal (<400 kcal, 20% fat). Co-administration of didanosine buffered tablet formulation with tenofovir should be under fasted conditions. **Co-administration of tenofovir and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse events. Didanosine should be discontinued in patients who develop didanosine-associated adverse events.**

Since tenofovir is primarily eliminated by the kidneys, co-administration of **Tenvor** 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 adefovir dipivoxil, cidofovir, acyclovir, valacyclovir, ganciclovir and valganciclovir.

Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders.

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

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

Table 2: Drug Interactions: Changes in Pharmacokinetics Parameters for Tenofovir[1] in the presence of the Co-administered drug Co-administered Drug

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

1. Patients received tenofovir 300 mg once daily.
2. Increase = up; Decrease = down; No Effect = ↔; NC = Not Calculated

Table 3: Drug Interactions: changes in pharmacokinetic parameters for co-administered drug in the presence of tenofovir

Co-administered Drug	Dose of Co-administered Drug (mg)	% Change of Co-administered Drug Pharmacokinetic Parameters [1] (90% CI)		
		C_{max}	AUC	C_{min}
Abacavir	300 once	Up 12 (down 1 to up 26)	↔	NA
Adefovir dipivoxil	10 once	↔	↔	NA
Efavirenz	600 once daily × 14 days	↔	↔	↔
Emtricitabine	200 once daily × 7 days	↔	↔	↔
Indinavir	800 three times daily × 7 days	Down 11 (down 30 to up 12)	↔	↔
Lamivudine	150 twice daily × 7 days	Down 24 (down 34 to down 12)	↔	↔
Lopinavir	Lopinavir/Ritonavir 400/100 twice daily × 14 days	↔	↔	↔
Methadone [2]	40-110 once daily × 14 days [3]	↔	↔	↔
Oral Contraceptives [4]	Ethinyl Estradiol/ Norgestimate Once daily × 7 days	↔	↔	↔
Ribavirin	600 once daily	↔	↔	NA
Ritonavir	Lopinavir/Ritonavir 400/100 twice daily × 14 days	↔	↔	↔
Atazanavir	400 once daily × 14 days	Down 21 (down 27 to down 14)	Down 25 (down 30 to down 19)	Down 40 (down 48 to down 32)
Atazanavir	Atazanavir/Ritonavir 300/100 once daily × 42 days	Down 28 (down 50 to up 5)	Down 25 [5] (down 42 to down 3)	Down 23 [5] (down 46 to up 10)

1. Increase = up; Decrease = down; No Effect = ↔; NA = Not Applicable
2. R-(active), S-and total methadone exposures were equivalent when dosed alone or with tenofovir.
3. Individual subjects were maintained on their stable methadone dose. No pharmacodynamic alterations (opiate toxicity or withdrawal signs or symptoms) were reported.
4. Ethinyl estradiol and 17-deacetyl norgestimate (pharmacologically active metabolite) exposures were equivalent when dosed alone or with tenofovir.
5. 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.

Table 4: Drug Interactions: Pharmacokinetics Parameters for Didanosine in the presence of tenofovir

Didanosine [1] Dose (mg)/ Method of Administration [2]	Tenofovir Method of Administration [2]	% 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	Up 28 (up 11 to up 48)	Up 44 (up 31 to up 59)
Enteric coated capsules			

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400 once, fasted	With food, 2 hr after didanosine	Up 48 (up 25 to up 76)	Up 48 (up 31 to up 67)
400 once, with food	Simultaneously with didanosine	Up 64 (up 41 to up 89)	Up 60 (up 44 to up 79)
250 once, fasted	With food, 2 hr after didanosine	Down 10 (down 22 to up 3)	↔
250 once, fasted	Simultaneously with didanosine	↔	Up 14 (0 to up 31)
250 once, with food	Simultaneously with didanosine	Down 29 (down 39 to down 18)	Down 11 (down 23 to up 2)

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

Side Effects

Clinical Trials: More than 12,000 patients have been treated with tenofovir alone or in combination with other antiretroviral medicinal products for periods of 28 days to 215 weeks in Phase I-III clinical trials and expanded access studies. A total of 1,287 patients have received tenofovir 300 mg once daily in Phase I-III clinical trials; over 11,000 patients have received tenofovir in expanded access studies.

Treatment-Naive Patients

Treatment-Emergent Adverse Events: The most common adverse reactions seen in a double-blind comparative controlled study in which 600 treatment-naïve patients received TDF (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, diarrhoea and nausea. Selected treatment-emergent moderate to severe adverse events are summarized in Table 5.

Table 5: Selected Treatment-Emergent Adverse events (grades 2-4) reported in >/=3% in any treatment group in study 903 (0-144 weeks)

	Tenofovir+3TC+EFV N=299	d4T + 3TC + EFV 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		
Diarrhoea	11%	13%
Nausea	8%	9%
Dyspepsia	4%	5%
Vomiting	5%	9%
Metabolic disorders		
Lipodystrophy [1]	1%	8%
Musculoskeletal		
Arthralgia	5%	7%
Myalagia	3%	5%
Nervous System		
Depression	11%	10%
Insomnia	5%	8%
Dizziness	3%	6%
Anxiety	6%	6%
Peripheral neuropathy[2]	1%	5%
Respiratory		
Pneumonia	5%	5%
Skin and Appendages		
Rash Event[3]	18%	12%

1. Lipodystrophy represents a variety of investigator-described adverse events not a protocol-defined syndrome
2.Peripheral neuropathy includes peripheral neuritis and neuropathy
3.Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash.

Laboratory Abnormalities: With the exception of triglyceride elevations that were more common in the stavudine group (8%) compared with tenofovir (2%), laboratory abnormalities observed in this study occurred with similar frequency in the tenofovir and stavudine treatment arms. A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 6.

Table 6: Grade 3 / 4 Laboratory Abnormalities reported in ≥ 1% of tenofovir-treated patients in study 903 (0-144 weeks)

	Tenofovir + 3TC + EFV N=299	d4T + 3TC + EFV N=301
Any = Grade 3 laboratory abnormality	36%	42%
Total cholesterol (>300 mg/dL)	5%	15%
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/mm³)	3%	1%
Triglyceride (>750 mg/dL)	3%	14%

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, diarrhoea, 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 events (grades 2-4) reported in ≥3% in any treatment group in study 907 (0-48 weeks)

	Tenofovir (N=368) (week 0-24)	Placebo (N=182) (week 0-24)	Tenofovir (N=368) (week 0-48)	Placebo crossover to tenofovir (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				
Diarrheoa	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 [1]	3%	3%	5%	2%
Dizziness	1%	3%	3%	1%
Skin and Appendage				
Rash Event [2]	5%	4%	7%	1%
Sweating	3%	2%	3%	1%
Musculoskeletal				
Myalgia	3%	3%	4%	1%
Metabolic				
Weight Loss	2%	1%	4%	2%

1.Peripheral neuropathy includes peripheral neuritis and neuropathy.
2.Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash.

Laboratory Abnormalities: Laboratory abnormalities observed in this study occurred with similar frequency in the tenofovir 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-treated Patients in Study 907 (0–144 weeks)

	Tenofovir (N=368) (week 0-24)	Placebo (N=182) (week 0-24)	Tenofovir (N=368) (week 0-48)	Placebo crossover to tenofovir (N=170) (week 24-48)
Any ≥ Grade 3 Laboratory Abnormality	25%	38%	35%	34%
Triglycerides (>750 mg/dL)	8%	13%	11%	9%
Creatine Kinase 7% (M: >990U/L) (F: >845 U/L)	14%	12%	12%	
Serum Amylase (>175 U/L)	6%	7%	7%	6%
Urine Glucose(>/=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 mg/dL)	1%	1%	2%	1%

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

Immune System Disorders: Allergic reaction

Metabolism and Nutrition Disorders: Hypophosphataemia, Lactic acidosis

Respiratory, Thoracic, and Mediastinal Disorders: Dyspnoea

Gastrointestinal Disorders: Abdominal pain, Pancreatitis

Hepatobiliary Disorders: Increased liver enzymes, Hepatitis

Renal and Urinary Disorders: Renal insufficiency, Renal failure, Acute renal failure, Fanconi syndrome, Proximal tubulopathy, Proteinuria, Increased creatinine, Acute tubular necrosis, Nephrogenic diabetes insipidus

Overdosage

Limited clinical experience at doses higher than the therapeutic dose of tenofovir 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, a four-hour haemodialysis session removed approximately 10% of the administered tenofovir dose.

Pharmacology

Pharmacodynamics

Mechanism of Action: 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 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, beta, and mitochondrial DNA polymerase gamma.

Pharmacokinetics

The pharmacokinetics of tenofovir disoproxil fumarate have been evaluated in healthy volunteers and HIV-1 infected individuals. Tenofovir pharmacokinetics are 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 296 ± 90 ng/mL and 2287 ± 685 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 disoproxil fumarate following a high-fat meal (~700 to 1000 kcal containing 40 to 50% fat) increases the oral bioavailability, with an increase in tenofovir AUC_{∞} of approximately 40% and an increase in Cmax of approximately 14%. However, administration of tenofovir disoproxil fumarate 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 326 ± 119 ng/mL and 3324 ± 1370 ng·hr/mL following multiple doses of tenofovir disoproxil fumarate 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 ± 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.

Packing

Packaging information

Tenvor Container of 30 tablets

Storage and handling instructions

Store below 30°C.

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