Tenofo-B™

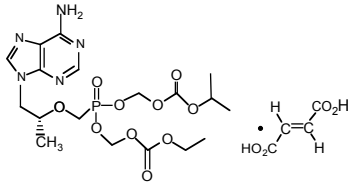
(Tenofovir Disoproxil Fumarate)

ٹینوفو-بی

300mg Film-Coated Tablets

DESCRIPTION

Tenofovir disoproxil fumarate is a salt of a prodrug of tenofovir. Tenofovir disoproxil fumarate is designated chemically as 9-[(*R*)-2 [[bis[[(isopropoxycarbonyl)oxy]methoxy]-phosphinyl]methoxy]propyl]adenine fumarate (1:1).The molecular formula is $C_{23}H_{34}O_{14}N_5P$ and the structural formula is



Tenofovir Disoproxil Fumarate

QUALITATIVE & QUANTITATIVE COMPOSITION

TENOFO-B (Tenofovir disoproxil fumarate) is available for oral administration as:

TENOFO-B Tablets 300mg
Each film-coated tablet contains:
Tenofovir disoproxil fumarate … 300mg
(Equivalent to 245mg of Tenofovir disoproxil)

CLINICAL PHARMACOLOGY

Mechanism of Action

Tenofovir disoproxil fumarate is the fumarate salt of the prodrug tenofovir disoproxil. Tenofovir disoproxil is absorbed and converted to the active substance tenofovir, which is a nucleoside monophosphate (nucleotide) analogue. Tenofovir is then converted to the active metabolite, tenofovir diphosphate, an obligate chain terminator, by constitutively expressed cellular enzymes. Tenofovir diphosphate has an intracellular half-life of 10 hours in activated and 50 hours in resting peripheral blood mononuclear cells (PBMCs). Tenofovir diphosphate inhibits HIV1 reverse transcriptase and the HBV polymerase by direct binding competition with the natural deoxyribonucleotide substrate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of cellular polymerases α, β, and γ. At concentrations of up to 300µmol/L, tenofovir has also shown no effect on the synthesis of mitochondrial DNA or the production of lactic acid in *in vitro* assays.

Pharmacokinetics

Tenofovir disoproxil fumarate is rapidly absorbed and converted to tenofovir following oral administration, with peak plasma concentration occurring after 1 to 2 hours. Bioavailability in fasting patients is reported to be 25% but this is enhanced when tenofovir disoproxil fumarate is taken with a high fat meal. Tenofovir is widely distributed into body tissues, particularly the kidneys and liver. Binding to plasma proteins is reported to less than 1% and that to serum proteins about 7%. The terminal elimination half-life is 12-18 hours. Tenofovir is excreted mainly in the urine by both active tubular secretion and glomerular filtration. It is removed by hemodialysis.

Special population

Renal Insufficiency

The pharmacokinetics of tenofovir are altered in patients with renal impairment. In non-HIV and non-HBV infected patients with creatinine clearance <50mL/min or with end-stage renal disease (ESRD) requiring dialysis, C_{max}, and $AUC_{0-\infty}$ of tenofovir were increased. Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%.

INDICATIONS

TENOFO-B (Tenofovir disoproxil fumarate) is indicated:

- In combination with at least two other antiretroviral agents for the management of HIV infected adults.
- For the treatment of chronic hepatitis B in adults with compensated liver disease, with evidence of active viral replication, persistant elevated serum alanine aminotransferase (ALT) level and histological evidence of active inflammation and fibrosis.

DOSAGE & ADMINISTRATION

Adults: The recommended dose for the treatment of HIV or for the treatment of chronic hepatitis B is 300mg (one tablet) once daily taken orally with food.

Chronic hepatitis B: The optimal duration of treatment is unknown. Treatment discontinuation may be considered as follows:

- In HBeAg positive patients without cirrhosis, treatment should be administered for at least 6-12 months after HBe seroconversion (HBeAg loss and HBV DNA loss with antiHBe detection) is confirmed or until HBs seroconversion or there is loss of efficacy. Serum ALT and HBV DNA levels should be followed regularly after treatment discontinuation to detect any late virological relapse.
- In HBeAg negative patients without cirrhosis, treatment should be administered at least until HBs seroconversion or there is evidence of loss of efficacy. With prolonged treatment for more than 2 years, regular reassessment is recommended to confirm that continuing the selected therapy remains appropriate for the patient.

Renal insufficiency:

No dose adjustment is necessary for patients with mild renal impairment (creatinine clearance 50–80mL/min). Routine monitoring of creatinine clearance and serum phosphorus should be performed in patients with mild renal impairment. Given below are the recommended dosing guidelines:

	Creatinine Clearance (mL/min)[a]			Hemodialysis Patients
	≥ 50	30-49	10-29	
Recommended 300mg dosing interval	Every 24 hours	Every 48 hours	Every 72 to 96 hours	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 3 hemodialysis sessions a week of approximately 4 hours duration. TENOFO-B (Tenofovir disoproxil fumarate) should be administered following completion of dialysis.

No dosing recommendation is available for patients with creatinine clearance <10mL/min.

ADVERSE REACTIONS

The most common adverse effects reported from the use of tenofovir disoproxil fumarate are mild gastrointestinal effects particularly diarrhea, nausea and anorexia. Serum-amylase concentrations may be raised and pancreatitis has occurred. Hypophosphatemia occurs commonly. Skin rashes may occur. Other adverse effects occurring commonly include peripheral neuropathy, headache, dizziness, insomnia, depression, asthenia, sweating and myalgia. There have been reports of raised liver enzymes, hypertriglyceridemia, hyperglycemia and neutropenia. There have also been reports of renal impairment, acute renal failure, and effects on the renal proximal tubules, including Fanconi Syndrome.

Lactic acidosis, usually associated with severe hepatomegaly and steatosis, has been associated with treatment with nucleoside reverse transcriptase inhibitors.

CONTRAINDICATIONS

- Tenofovir disoproxil fumarate is contraindicated in patients with known hypersensitivity to tenofovir or to any of the components

of the formulation.
- It should not be administered concurrently with other tenofovir containing combinations formulation or with adefovir dipivoxil.
- Tenofovir disoproxil fumarate is not recommended for use in children below the age of 18 years.

WARNINGS

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 disoproxil fumarate, in combination with other antiretrovirals.
- 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 disoproxil fumarate. If appropriate, resumption of anti-hepatitis B therapy may be warranted.

Treatment with tenofovir disoproxil fumarate should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

PRECAUTIONS

General
- Patients receiving tenofovir disoproxil fumarate or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with HIV associated diseases.
- Patients should be advised that antiretroviral therapies, including TENOFO-B, have not been proven to prevent the risk of transmission of HIV or HBV to others through sexual contact or blood contamination. Appropriate precautions must continue to be used.
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
- Tenofovir disoproxil fumarate may be associated with reduction in bone density and patients should be observed for evidence of bone abnormalities.

Geriatric Patients
Dose selection for the elderly patients should be done with caution, keeping in mind the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Renal Insufficiency
It is recommended that creatinine clearance is calculated in all patients prior to initiating therapy and as clinically appropriate, during tenofovir disoproxil fumarate therapy. Patients at risk for, or with a history of, renal dysfunction should be routinely monitored for changes in serum creatinine and phosphorus.

Hepatic Insufficiency
- Patients with cirrhosis may be at a higher risk for hepatic decompensation following hepatitis exacerbation and therefore should be monitored closely during therapy.
- Co-infected patients with HIV and hepatitis B: Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Liposystrophy (lipoatrophy/lipomatosis) Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

Immune Reactivation Syndrome
Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Osteonecrosis
Patients are advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

DRUG INTERACTIONS
Didanosine: Co-administration of tenofovir disoproxil fumarate 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.

Atazanavir: Tenofovir disoproxil fumarate affects the pharmacokinetics of atazanavir. Tenofovir disoproxil fumarate should only be administered with boosted atazanavir (ATZ 300mg/RTV 100mg).

Triple therapy with nucleoside/necleotides: High rates of virological failure and of emergence of resistance at early stage in HIV patients occurred when tenofovir disoproxil fumarate was combined with lamivudine and abacavir as well as lamivudine and didanosine as a once daily regimen. Patients on a therapy utilizing a triple nucleoside-only regimen should be carefully monitored and considered for treatment modification.

Tracolimus/Other medicinal products affecting renal function: Since tracrolimus can affect renal function, close monitoring is recommended when it is co-administered with tenofovir disoproxil fumarate. Co-administration of tenofovir disoproxil fumarate with other medicinal products that decrease or compete for renal clearance may increase serum concentrations of tenofovir disoproxil fumarate.

HIV and HBV co-infection:
Due to the risk of development of HIV resistance, tenofovir disoproxil fumarate should only be used as part of an appropriate antiretroviral combination regimen in HIV/HBV co-infected patients.

Pregnancy
Tenofovir disoproxil fumarate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Given that the potential risks to the developing fetus are unknown, the use of tenofovir disoproxil fumarate in women of childbearing potential must be accompanied by the use of effective contraception.

Nursing Mothers
It is not known whether tenofovir disoproxil fumarate is excreted in human milk. It is therefore recommended that mothers being treated with tenofovir disoproxil fumarate do not breast-feed their infants.

As a general rule, it is recommended that HIV and HBV infected women do not breast-feed their infants in order to avoid transmission of HIV and HBV to the infant.

STORAGE
Store below 25°C.
Protect from sunlight and moisture.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
TENOFO-B (Tenofovir disoproxil fumarate) Tablets 300mg are available in a bottle of 30's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

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