Tenofomide™

[Tenofovir Alafenamide]

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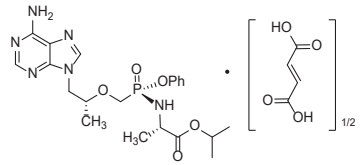
Tablets 25mg

DESCRIPTION

Tenofomide contains Tenofovir alafenamide, a hepatitis B virus (HBV) nucleoside analog reverse transcriptase inhibitor, which is converted *invivo* to Tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate. Chemically, Tenofovir alafenamide fumarate is L-alanine, N-[(S)-[[(1R)-2-(6-amino -9H-purin-9-yl)-1-methylethoxy]methyl]phenoxyphosphinyl]-, 1methylethyl ester, (2E)-2-butenedioate (2:1). Its molecular formula is $C_{21}H_{29}O_5N_6P•½(C_4H_4O_4)$ and the structural formula is:



Tenofovir alafenamide fumarate

QUALITATIVE AND QUANTITATIVE COMPOSITION

Tenofomide (Tenofovir alafenamide) Tablets are available for oral administration as:

Tenofomide Tablets 25mg
Each film-coated tablet contains:
Tenofovir alafenamide fumarate equivalent to
Tenofovir alafenamide…25mg

CLINICAL PHARMACOLOGY

Mechanism of Action

Tenofovir alafenamide is a phosphonamidate prodrug of Tenofovir (2'-deoxyadenosine monophosphate analog). Tenofovir alafenamide as a lipophilic cell-permeant compound enters primary hepatocytes by passive diffusion and by the hepatic uptake transporters OATP1B1 and OATP1B3. Tenofovir alafenamide is then converted to Tenofovir through hydrolysis primarily by carboxylesterase 1 (CES1) in primary hepatocytes. Intracellular Tenofovir is subsequently phosphorylated by cellular kinases to the pharmacologically active metabolite Tenofovir diphosphate. Tenofovir diphosphate inhibits HBV replication through incorporation into viral DNA by the HBV reverse transcriptase, which results in DNA chain-termination.
Tenofovir has activity that is specific to hepatitis B virus and human immunodeficiency virus (HIV-1 and HIV-2). Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there is no evidence of toxicity to mitochondria in cell culture.

Pharmacokinetics

Absorption
Following oral administration of Tenofovir alafenamide under fasted conditions in adult patients with chronic hepatitis B, peak plasma concentrations were observed approximately 0.48 hours post-dose. The steady-state mean C_{max} and AUC_{last} for Tenofovir alafenamide were 0.25 ± 0.11 µg/ml and 0.15 ± 0.06 µg•hr/ml, respectively. Relative to fasting conditions, the administration of a single dose of Tenofovir alafenamide with a high fat meal resulted in a 65% increase in its exposure.

Distribution
The binding of Tenofovir to human plasma proteins is less than 0.7% and is independent of concentration over the range of 0.01–25 µg/ml. The binding of Tenofovir alafenamide to human plasma proteins in samples collected during clinical trials was approximately 80%.

Metabolism
Metabolism is a major elimination pathway for Tenofovir alafenamide in humans, accounting for > 80% of an oral dose. *Invitro* studies have shown that Tenofovir alafenamide is metabolized to Tenofovir (major metabolite) by carboxylesterase-1 in hepatocytes; and by cathepsin A in PBMCs and macrophages. *Invivo,* Tenofovir alafenamide is hydrolysed within cells to form Tenofovir (major metabolite), which is phosphorylated to the active metabolite, Tenofovir diphosphate. Tenofovir alafenamide is minimally metabolized by CYP3A4.

Elimination
Tenofovir alafenamide is eliminated following metabolism to Tenofovir. Tenofovir alafenamide and Tenofovir have a median plasma half-life of 0.51 and 32.37 hours, respectively. Tenofovir is renally eliminated by both glomerular filtration and active tubular secretion. Unlike Tenofovir, Tenofovir alafenamide is not a substrate for the renal transporters OAT1 and OAT3. Renal excretion of intact Tenofovir alafenamide is a minor pathway with less than 1% of the dose eliminated in urine. The pharmacologically active metabolite, Tenofovir diphosphate, has a half-life of 150-180 hours within PBMCs.

Special population

Patients with Renal Impairment
No clinically relevant differences in Tenofovir alafenamide or Tenofovir pharmacokinetics were observed between healthy subjects and patients with severe renal impairment (estimated CrCl > 15 but < 30 mL/min). Relative to patients with normal renal function (estimated creatinine clearance ≥ 90 mL/min), the Tenofovir alafenamide and Tenofovir systemic exposures in patients with severe renal impairment were 1.9-fold and 5.7-fold higher respectively.

Patients with Hepatic Impairment
Relative to subjects with normal hepatic function, Tenofovir alafenamide and Tenofovir systemic exposures were 7.5% and 11% lower in subjects with mild hepatic impairment, respectively.

THERAPEUTIC INDICATIONS

Tenofomide (Tenofovir alafenamide) is indicated for the treatment of chronic hepatitis B virus (HBV) infection in adults and adolescents (aged 12 years or above having body weight at least 35 kg).

DOSAGE AND ADMINISTRATION

Recommended Dosing
The recommended dose of Tenofomide (Tenofovir alafenamide) is 25mg once daily. Tenofomide (Tenofovir alafenamide) Tablets may be taken with or without food.

Patients with renal impairment
No dosage adjustment of Tenofomide (Tenofovir alafenamide) is required in patients with mild, moderate, or severe renal impairment. Tenofomide (Tenofovir alafenamide) is not recommended in patients with end stage renal disease (estimated creatinine clearance below 15 mL per minute).

Patients with hepatic impairment
No dosage adjustment of Tenofomide (Tenofovir alafenamide) is required in patients with mild hepatic impairment (Child-Pugh A). Tenofomide (Tenofovir alafenamide) is not recommended in patients with decompensated (Child- Pugh B or C) hepatic impairment.

Elderly
No dose adjustment of Tenofomide (Tenofovir alafenamide) is required in patients aged 65 years and older.

Treatment Discontinuation
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 anti-HBe detection) is confirmed or until HBs seroconversion or until there is loss of efficacy. Regular reassessment is recommended after treatment discontinuation to detect virological relapse.
- In HBeAg-negative patients without cirrhosis, treatment should be administered at least until HBs seroconversion or until 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.

Missed Dose
If a dose is missed and less than 18 hours have passed from the time it is usually taken, the patient should take Tenofomide (Tenofovir alafenamide) as soon as possible and then resume their normal dosing schedule. If more than 18 hours have passed from the time it is usually taken, the patient should not take the missed dose and should simply resume the normal dosing schedule. If the patient vomits within 1 hour of taking Tenofomide (Tenofovir alafenamide), the patient should take another tablet. If the patient vomits more than 1 hour after taking Tenofomide (Tenofovir alafenamide), the patient does not need to take another tablet.

CONTRAINDICATIONS

Tenofovir alafenamide is contraindicated in patients with hypersensitivity to active substance or to any excipient of the product.

ADVERSE REACTIONS

Very common
Headache.

Common
Dizziness, rash, pruritus, increased ALT, arthralgia, diarrhea, vomiting, nausea, abdominal pain, abdominal distension, flatulence, fatigue and cough.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's Pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

WARNINGS AND PRECAUTIONS

Severe Acute Exacerbation of Hepatitis B after Discontinuation of Treatment

Discontinuation of anti-hepatitis B therapy, including Tenofovir alafenamide, may result in severe acute exacerbations of hepatitis B. Patients who discontinue Tenofovir alafenamide 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.

Risk of Development of HIV-1 Resistance in Patients Coinfected with HBV and HIV-1
Due to the risk of development of HIV-1 resistance, Tenofovir alafenamide alone is not recommended for the treatment of HIV-1 infection. The safety and efficacy of Tenofovir alafenamide is not established in patients coinfected with HBV and HIV-1. HIV antibody testing should be offered to all HBV-infected patients before initiating therapy with Tenofovir alafenamide, if positive an appropriate antiretroviral combination regimen that is recommended for patients coinfected with HIV-1 should be used.

New Onset or Worsening Renal Impairment
Patients taking Tenofovir prodrugs who have impaired renal function and those taking nephrotoxic agents, including non-steroidal anti-inflammatory drugs are at increased risk of developing renal-related adverse reactions. It is recommended that serum creatinine, serum phosphorous, estimated creatinine clearance, urine glucose and urine protein be assessed before initiating Tenofovir alafenamide and during therapy in all patients as clinically appropriate. Discontinue Tenofovir alafenamide in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

HBV Transmission
Patients must be advised that Tenofovir alafenamide does not prevent the risk of transmission of HBV to others through sexual contact or contamination with blood. Appropriate precautions must continue to be used.

Nephrotoxicity
Potential risk of nephrotoxicity resulting from chronic exposure to low levels of Tenofovir due to dosing with Tenofovir alafenamide cannot be excluded.

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. Treatment with Tenofovir alafenamide 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 with decompensated liver disease
HBV-infected patients with decompensated liver disease and who have a Child Pugh Turcotte (CPT) score > 9 (i.e. class C) may be at higher risk of experiencing serious hepatic or renal adverse reactions. Therefore, hepatobiliary and renal parameters should be closely monitored in this patient population.

Exacerbation of Hepatitis
Spontaneous exacerbations in chronic hepatitis B are relatively common and are characterized by transient increases in serum alanine aminotransferase (ALT). Patients with cirrhosis may be at a higher risk for hepatic decompensation following hepatitis exacerbation and therefore should be monitored closely during therapy. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation. Liver flares are especially serious and sometimes fatal in patients with decompensated liver disease.

Lactose Intolerance
Tenofovir alafenamide tablet contains lactose monohydrate. Consequently, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

Effects on ability to drive and use machines
Tenofovir alafenamide has no or negligible influence on the ability to drive and use machines. Patients should be alerted that dizziness occurs during treatment with Tenofovir alafenamide.

Pregnancy
There are no adequate and well-controlled studies with Tenofovir alafenamide in pregnant women. Tenofovir alafenamide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is unknown whether Tenofovir alafenamide is secreted in human milk. A risk to the breastfed child cannot be excluded; therefore, Tenofovir alafenamide should not be used during breast-feeding.

DRUG INTERACTION
Potential for Other Drugs affecting Tenofovir alafenamide
Tenofovir alafenamide is a substrate of P-glycoprotein (P-gp) and BCRP. Drugs that strongly affect P-gp and BCRP activity may lead to changes in Tenofovir alafenamide absorption. Drugs that induce P-gp activity are expected to decrease the absorption of Tenofovir alafenamide, resulting in decreased plasma concentrations of Tenofovir alafenamide, which may lead to loss of therapeutic efficacy. Co-administration of Tenofovir alafenamide with other drugs that inhibit P-gp and BCRP may increase the absorption and plasma concentration of Tenofovir alafenamide.

Drugs affecting Renal function
Co-administration of Tenofovir alafenamide with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of Tenofovir and other renally eliminated drugs and this may increase the risk of adverse reactions. Some examples of drugs that are eliminated by active tubular secretion include, but are not limited to, acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs.

Co-administration with other medicinal products
Tenofovir alafenamide should not be co-administered with products containing Tenofovir alafenamide, Tenofovir disoproxil fumarate or Adefovir dipivoxil. Co-administration of Tenofovir alafenamide is not recommended with certain anticonvulsants (e.g. carbamazepine, oxcarbazepine, phenobarbital and phenytoin), antimycobacterials (e.g. rifampicin, rifabutin and rifapentine) or St. John's wort, all of which are inducers of P-glycoprotein (P-gp) and may decrease Tenofovir alafenamide plasma concentrations.

OVERDOSAGE
In the event of an overdose, the patient must be monitored for evidence of toxicity. Treatment of overdose with Tenofovir alafenamide consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient. Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. It is not known whether Tenofovir can be removed by peritoneal dialysis.

STORAGE
Do not store above 30°C.
Protect from sunlight and moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
Tenofomide (Tenofovir alafenamide) Tablets 25mg 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.

Manufactured by:
Getz pharma (PVT) LIMITED
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