Front

Tenovir®

(Tenofovir Disoproxil Fumarate)

300 mg
Tablet

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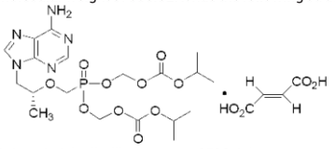
COMPOSITION:
Each film coated tablet contains:
Tenofovir Disoproxil Fumarate ..... 300 mg.

Product Specs.: CCL Pharmaceuticals

DESCRIPTION:
TENOVIR is the brand name for tenofovir DF (a prodrug of tenofovir) which is a fumaric acid salt of bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. It has a molecular formula of $C_{23}H_{34}N_5O_{14}P.C_4H_4O_4$ and a molecular weight of 635.52. It has the following structural formula:



Tenofovir has solubility of 13.4 mg/mL in distilled water at 25ºC. It has an octanol/phosphate buffer (pH 6.5) partition coefficient (log p) of 1.25 at 25ºC.

CLINICAL PHARMACOLOGY:
Mechanism of action:
Tenofovir DF is an antiviral drug. Tenofovir DF is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir DF requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate, an obligate chain terminator.
Activity Against HIV:
Antiviral activity: The antiviral activity of tenofovir against isolates of HIV-1 in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes showed that the EC50 (50% effective concentration) values for tenofovir were in the range of 0.04-8.5μM Tenofovir is not antagonistic with nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir).
Resistance: HIV-1 isolates with reduced susceptibility to tenofovir selected in cell culture express that a K65R substitution in reverse transcriptase and show a 2 to 4 fold reduction in susceptibility to tenofovir. In addition, a K70E substitution in HIV-1 reverse transcriptase has been selected by tenofovir and results in low-level reduced susceptibility to tenofovir.
Cross resistance: Cross resistance among certain reverse transcriptase inhibitors has been recognized. The K65R and K70E substitutions selected by tenofovir are also selected in some HIV-1 infected subjects treated with abacavir or didanosine. HIV-1 isolates with this substitution also show reduced susceptibility to emtricitabine and lamivudine.
Activity Against HBV:
Antiviral activity: The antiviral activity of tenofovir against HBV in the HepG2 2.2.15 cell line shows that the EC50 values for tenofovir ranged from 0.14 to 1.5 M, with CC50 (50% cytotoxicity concentration) values greater than 100 M. Resistance: HBV isolates from subjects who remain viremic show treatment-emergent substitutions however, no specific substitutions occurred at a sufficient frequency to be associated with resistance to tenofovir (genotypic and phenotypic analyses).
Cross resistance: Cross resistance has been observed between HBV nucleoside/nucleotide analogue reverse transcriptase inhibitors.
Pharmacokinetics:
Absorption: Tenofovir is a water soluble diester prodrug of the active ingredient tenofovir. The oral bioavailability of tenofovir from in fasted subjects is approximately 25%. The pharmacokinetics of tenofovir are dose proportional over a dose range of 75 to 600 mg and are not affected by repeated dosing.
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 g/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: Tenofovir disoproxil and tenofovir are not substrates of CYP 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, the terminal elimination half-life is approximately 17 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.
Effects of food on oral absorption: Administration of 300 mg tablets 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%. Food delays the time to tenofovir C_{max} by approximately 1 hour. C_{max} and AUC_0-of tenofovir are 0.33-0.12 g/mL and 3.32-1.37 g hr/mL upon multiple doses of tenofovir 300 mg once daily in the fed state, when meal content was not controlled.
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 subjects.
Pediatric patients 2 years of age and older: Tenofovir exposure in these pediatric subjects receiving oral once daily doses of 300 mg (tablet) or 8 mg/kg of body weight is similar to exposures in adults receiving once-daily doses of 300 mg.
Geriatric patients: Pharmacokinetic trials have not been performed in the elderly (65 years and older).
Patients with impaired renal function: The pharmacokinetics of tenofovir in subjects with creatinine clearance below 50 mL/min or with end-stage renal disease (ESRD) requiring dialysis, C_{max}, and AUC of tenofovir increase. It is recommended that the dosing interval for tenofovir be modified in patients with estimated creatinine clearance below 50 mL/min or in patients with ESRD who require dialysis.
Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%.
Patients with hepatic impairment: The pharmacokinetics of tenofovir following a 300 mg in non-HIV infected subjects with moderate to severe hepatic impairment show no substantial alterations in tenofovir pharmacokinetics as compared with unimpaired subjects. No change in tenofovir dosing is required in patients with hepatic impairment.

INDICATIONS AND USAGE:
- Indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients 2 years of age and older.
- Indicated for the treatment of chronic hepatitis B in adults and pediatric patients 12 years of age and older.

DOSAGE AND ADMINISTRATION:
Adult dosage:
Recommended dose for the treatment of HIV-1 or chronic hepatitis B in adults and pediatric patients 12 years of age and older (35 kg or more) 300 mg once daily taken orally without regard to food.
Pediatric dosage:
Recommended dose for the treatment of HIV-1 in pediatric patients (2 to less than 12 years of age) one **TENOVIR** tablet (based on body weight) once daily taken orally without regard to food.

DOSE MODIFICATION RECOMMENDATIONS:
Renal impairment in adults:
- **Creatinine clearance 30–49 mL/min:** 300 mg every 48 hours.
- **Creatinine clearance 10–29 mL/min:** 300 mg every 72 to 96 hours.
- **Hemodialysis:** 300 mg every 7 days or after approximately 12 hours of dialysis.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS:
New onset or worsening renal impairment:
Can include acute renal failure and Fanconi syndrome. Assess estimated creatinine clearance before initiating treatment with **TENOVIR**. In patients at risk for renal dysfunction, assess estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein before initiating treatment with **TENOVIR** and periodically during treatment. Avoid administering **TENOVIR** with concurrent or recent use of nephrotoxic drugs.
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 in litreature, including tenofovir DF, alone or in combination with other antiretrovirals. Discontinue treatment in patients who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity.
Patients Co-infected with HIV-1 and HBV: Due to the risk of development of HIV-1 resistance, **TENOVIR** should only be used in HIV-1 and HBV co-infected patients as part of an appropriate antiretroviral combination regimen. It is also recommended that all patients with HIV-1 be tested for the presence of chronic hepatitis B before initiating treatment with **TENOVIR.**
Co-administration with other products: Do not use with other tenofovir containing products.
Immune reconstitution syndrome: During the initial phase of combination antiretroviral treatment, HIV-infected 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) and may necessitate further evaluation and treatment.
Virologic failure with triple nucleoside-only regimens: Early virologic failure has been reported in HIV-infected patients. Monitor carefully and consider treatment modification. Triple nucleoside regimens should therefore be used with caution.
Decreases in bone mineral density (BMD): Consider assessment of BMD in patients with a history of pathologic fracture or other risk factors for osteoporosis or bone loss.
Recommended Laboratory Tests:
HIV testing: HIV antibody testing should be offered to all HBV-infected patients before initiating therapy with **TENOVIR**. **TENOVIR** should only be used as part of an appropriate antiretroviral combination regimen in HIV-infected patients with or without HBV coinfection.

DRUG INTERACTIONS:
Didanosine: When administered with **TENOVIR**, C_{max} and AUC of didanosine increased significantly. Didanosine should be discontinued in case of adverse reactions. For additional information please refer to the full prescribing information for didanosine.
HIV-1 Protease Inhibitors: Tenofovir decreases the AUC and Cmin of atazanavir. When co-administered with Tenofovir, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg and should not be co-administered with atazanavir without ritonavir. Lopinavir/ritonavir, atazanavir coadministered with ritonavir, and darunavir co-administered with ritonavir have been shown to increase tenofovir concentrations. Tenofovir DF is a substrate of P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP) transporters. When tenofovir DF is co-administered with an inhibitor of these transporters, an increase in absorption may be observed.
Hepatitis C antiviral agents: Co-administration with combination therapy (sofosbuvir/velpatasvir) or (ledipasvir/sofosbuvir) has been shown to increase tenofovir exposure when used in combination, monitor for adverse reactions associated with tenofovir DF.
Drugs affecting renal function: 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 e.g. cidofovir, acyclovir, valacyclovir, ganciclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs. In the treatment of chronic hepatitis B, **TENOVIR** should not be administered in combination with adefovir dipivoxil.

USE IN SPECIFIC POPULATIONS:
Pregnancy Category B: In the absence of adequate and well-controlled studies in pregnant women **TENOVIR** should be used during pregnancy only if clearly needed.
Nursing mothers: Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving **TENOVIR**.
Pediatric use: Safety and effectiveness of **TENOVIR** in pediatric Patients 2 Years of Age and Older with HIV-1 infection and Pediatric Patients 12 Years of Age and Older with Chronic Hepatitis B patients have not been established.
Geriatric use: 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 renal impairment: It is recommended that the dosing interval for **TENOVIR** be modified in patients with estimated creatinine clearance below 50 mL/min or in patients with ESRD who require dialysis

ADVERSE REACTIONS:
In HIV-infected adult subjects: Most common adverse reactions (incidence greater than or equal to 10%, Grades 2–4) are rash, diarrhea, headache, pain, depression, asthenia, and nausea.
In HBV-infected subjects with compensated liver disease: Most common adverse reaction (all grades) was nausea (9%)
In pediatric subjects:
Adverse reactions in pediatric subjects were consistent with those observed in adults In HBV-infected subjects with decompensated liver disease: Most common adverse reactions (incidence greater than or equal to 10%, all grades) were abdominal pain, nausea, insomnia, pruritus, vomiting, dizziness, and pyrexia.

OVERDOSAGE:
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 hemodialysis with an extraction coefficient of approximately 54%.

INSTRUCTIONS:
- Store below 30ºC.
- Protect from heat, sunlight & moisture.
- Keep out of the reach of children.
- To be sold on the prescription of a registered medical practitioner only.

PRESENTATION:
TENOVIR Tablet 300 mg : Pack of 3 x 10 tablets.

ہدایات:
۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔
صرف ڈاکٹر کے نسخہ پر فروخت کریں۔

FOR FURTHER INFORMATION PLEASE CONTACT:

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