PRESCRIBING INFORMATION
Tenofovir Disoproxil Fumarate & Lamivudine Tablets

TUDOBEST-L™

GENERIC NAME:
Tenofovir Disoproxil Fumarate 300mg & Lamivudine 300mg Tablets

COMPOSITION:
Each film coated tablet contains
Tenofovir disoproxil fumarate 300mg
Lamivudine. 300mg
Colour: Indigo Carmine & Titanium Dioxide

PHARMACOLOGICAL ACTION: Tenofovir disoproxil fumarate

Mechanism of Action Tenofovir Disoproxil fumarate is an antiviral drug.

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 is a water soluble diester prodrug of the active ingredient tenofovir. The oral bioavailability of tenofovir from Tenofovir in fasted subjects is approximately 25%. The pharmacokinetics of tenofovir are dose proportional over a Tenofovir 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 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 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 of tenofovir 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.

Lamivudine Lamivudine is a selective inhibitor of HIV-1 and HIV-2 replication *in vitro,* including zidovudine-resistant clinical isolates of the human immunodeficiency virus (HIV). Lamivudine is metabolised intracellularly to the active 5'-triphosphate which inhibits the RNA-and DNA-dependant activities of HIV reverse transcriptase by termination of the viral DNA chain. Lamivudine does not interfere with cellular deoxynucleotide metabolism and has little effect on mammalian cell and mitochondrial DNA content.. Reduced *in-vitro* sensitivity to lamivudine has been reported for HIV isolated from patients who have received lamivudine therapy before. Lamivudine has been shown to act additively or synergistically with other anti-HIV agents, particularly zidovudine, inhibiting the replication of HIV in cell culture. *In vitro* studies indicate that zidovudine-resistant virus isolates can become zidovudine-sensitive when they acquire resistance to lamivudine.

Pharmacokinetics: Pharmacokinetics in adults: Following oral administration, lamivudine is well absorbed with bioavailability of approximately 80%. The mean time (Tmax) to maximum serum concentration (Cmax) is about an hour. At therapeutic dose levels of 4 mg/kg/day (as two 12-hourly doses), Cmaxis in the order of 1-1.5 micrograms/mL. The mean volume of distribution from intravenous studies has been reported as 1.3 L/kg and the mean terminal half-life of elimination as 5 to 7 hours. The mean systemic clearance of lamivudine is approximately 0.32 L/kg/h, with predominantly renal clearance of more than 70% via active tubular secretion, but little hepatic metabolism, at less than 10 L. The intracellular half-life of the lamivudine triphosphate active metabolite is prolonged, averaging over 10 hours in peripheral blood lymphocytes. A delay in Tmax, and reduction in Cmax have been observed when co-administered with food, but no dose adjustment is needed, as lamivudine bioavailability is not altered. Lamivudine displays limited binding to albumin and exhibits linear pharmacokinetics over the therapeutic dose range. Co-administration of zidovudine results in a 13% increase in zidovudine exposure and a 28% increase in peak plasma levels. No dosage adjustments are necessary, as this is not considered to be of significance to patient safety.
Pharmacokinetics in children:

In general, lamivudine pharmacokinetics in paediatric patients are similar to adults. However, absolute bioavailability is reduced to approximately 65%, in paediatric patients, with an increased clearance of 0.52 L/kg/hr. There are limited pharmacokinetic data for patients <3 months of age.

INDICATIONS TENOFOVIR DISOPROXIL FUMARATE & LAMIVUDINE TABLETS is indicated as part of antiretroviral combination therapy for treatment of HIV infected adults and children.

CONTRA-INDICATIONS Hypersensitivity to any of the ingredients.

WARNINGS: Patients receiving Lamivudine, Tenofovir disoproxil fumarate and other antiretroviral agents may continue to develop opportunistic infections and other complications of HIV infection. Patients should therefore remain under close supervision by medical practitioners experienced in the treatment of patients with HIV-associated diseases.
Current antiretroviral therapy, including Lamivudine, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination.

INTERACTIONS: Zidovudine plasma levels are not significantly altered when co-administered with lamivudine (see Pharmacokinetics). An interaction with trimethoprim, a constituent of co-trimoxazole. causes a 40% increase in lamivudine plasma concentrations at therapeutic doses. This does not require dose adjustment unless the patient also has renal impairment. Administration of co-trimoxazole with the Lamivudine/zidovudine combinations in patients with renal impairment should be carefully assessed. lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicinal products are used concurrently.

PREGNANCY AND LACTATION: Safety in pregnancy and lactation has not been established

DOSAGE AND DIRECTIONS FOR USE: Adults and adolescents more than 12 years of age: The recommended dose of TENOFOVIR DISOPROXIL FUMARATE & LAMIVUDINE TABLETS is one tablet daily.
Children ≥3 months to 12 years of age:The recommended dose is 4 mg/kg twice daily up to a maximum of 300 mg daily.Children <3 months of age: There are limited data to propose specific dosage recommendations
TENOFOVIR DISOPROXIL FUMARATE & LAMIVUDINE TABLETS can be taken with or without food.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS: Tenofovir disoproxil fumarate The following adverse reactions have been identified during 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.

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.

Lamivudine
The following side-effects have been reported during therapy of HIV disease with Lamivudine alone, and in combination with other anti-retrovirals. Gastro-intestinal disorders:Pancreatitis, upper abdominal pain, nausea; vomiting and diarrhoea have been reported.
Blood and lymphatic system disorders:

Neutropenia, thrombocytopenia and anaemia have occurred.Skin and appendages disorders:Alopecia has been reported.Central and Peripheral Nervous system disorders:Peripheral neuropathy, paraesthesia, and headache have been reported.Musculo-skeletal system disorders:Arthralgia, muscle disorders including less frequently, rhabdomyolysis have been reported. Body as a whole: Malaise, fatigue and fever have occurred.

Hypersensitivity reactions: Skin rash.
Changes in laboratory test parameters:
Transient rises in serum liver enzymes (AST; ALT) and rises in serum amylase have been reported.

Special precautions: Lamivudine should be used with caution in patients with advanced cirrhotic liver disease due to chronic Hepatitis B infection, as there is a small risk of rebound hepatitis post treatment.

Pancreatitis: Pancreatitis has been observed in some patients receiving Lamivudine.
Lactic acidosis/severe hepatomegaly with steatosis:
Long-term use of Lamivudine can result in potentially fatal lactic acidosis. Diagnosis of lactic acidosis is confirmed by demonstrating metabolic acidosis with an increased anion gap and raised lactate level. Therapy should be stopped in any acidotic patient with raised lactate level.

Treatment with Lamivudine should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity. Opportunistic infections:Patients receiving Lamivudine may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close observation by medical practitioners experienced in the treatment of patients with associated HIV disease. The risk of HIV transmission to others:

Patients should be advised that current antiretroviral therapy, including Lamivudine, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Patients with moderate to severe renal impairment:

In patients with moderate to severe renal impairment, the terminal half-life of lamivudine is increased due to decreased clearance. The dose should therefore be adjusted
KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT: If overdose occurs the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.

SHELF LIFE: 24 months from the date of manufacturing..

PRESENTATION: 30 Tablets pack in HDPE bottle & is packed in an individual carton along with a package insert.

STORAGE INSTRUCTIONS: Store below 30ºC. Protect from light.

KEEP OUT OF REACH OF CHILDREN.

MARKETED BY:

APRAZER

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