PRESCRIBING INFORMATION
LAMIVUDINE Tablets 150mg

LAMIPURE™

GENERIC NAME:
LAMIVUDINE Tablets 150mg

COMPOSITION:
Each uncoated tablet contains:
Lamivudine 150 mg

PHARMACOLOGICAL CLASSIFICATION:
A 20.2.8 - Antiviral agents

PHARMACOLOGICAL ACTION:
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. *In vitro,* lamivudine demonstrates low cytotoxicity to peripheral blood lymphocytes, to established lymphocyte and monocyte-macrophage cell lines, and to a variety of bone marrow progenitor cells. *In vitro,* lamivudine therefore has a high therapeutic index. 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. Limited data shows lamivudine penetrates the central nervous system and reaches the cerebrospinal fluid (CSF). The true extent of penetration or relationship with any clinical efficacy is unknown.
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
LAMIVUDINE 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 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.

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of lamivudine alone or in combination, in the treatment of HIV infection.

INTERACTIONS
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. LAMIVUDINE is therefore not recommended to be used in combination with zalcitabine.

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 LAMIVUDINE is 300 mg daily. This may be administered as either 300 mg once daily or 150 mg twice daily.
The package insert for zidovudine must be consulted for information on its dosage and administration.
For patients with low body weights (less than 50 kg), the recommended oral dose of LAMIVUDINE is 2 mg/kg twice daily.
LAMIVUDINE can be taken with or without food.

Renal and Hepatic Impairment:
Renal impairment, whether disease- or age-related, affects lamivudine elimination. For recommended dosage regimens in patients with a creatinine clearance below 50 ml/min see table below.
Adults and adolescents >12 years of age:

Creatinine Clearance (mL/min)	Recommended dose of LAMIVUDINE
≥50	150 mg twice daily
30-49	150 mg once daily
15-29	150 mg first dose, then 100 mg once daily
5-14	150 mg first dose, then 50 mg once daily
<5	50 mg first dose, then 25 mg once daily

SIDE-EFFECTS AND SPECIAL PRECAUTIONS
Side-effects: 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. However it is unclear whether this is due to LAMIVUDINE or to underlying HIV disease. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of LAMIVUDINE until diagnosis of pancreatitis is excluded.

Lactic acidosis/severe hepatomegaly with steatosis:
Long-term use of LAMIVUDINE can result in potentially fatal lactic acidosis. Symptomatic hyperlactacaemia and lactic acidosis are uncommon. Clinical features are non-specific, and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss. Suspicious biochemical features include mild raised transaminases, raised lactate dehydrogenase (LDH) and/or creatine kinase.
In patients with suspicious symptoms or biochemistry. measure the venous lactate level (normal <2 mmol/L), and respond as follows:

Lactate 2 - 5 mmol/L: monitor regularly, and be alert for clinical signs.

Lactate 5 - 10 mmol/L without symptoms: monitor closely.

Lactate 5 - 10 mmol/L with symptoms: STOP all therapy. Exclude other causes (e.g. sepsis, uraemia. diabetic ketoacidosis, thyrotoxicosis, lymphoma).

Lactate 5 - 10 mmol/L: STOP all therapy (80% mortality in case studies).

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.

Blood for lactate assays should be heparinised and stored on ice.
After recovery, NRTI's should be avoided. Seek expert advice on medicine selection. The above lactate values may not be applicable to paediatric patients.

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of LAMIVUDINE alone or in combination, in the treatment of HIV infection. Most cases were women.

Caution should be exercised when administering LAMIVUDINE to patients with known risk factors for liver disease

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:
Treatment is symptomatic and supportive.

SHELF LIFE : Refer label for the shelf life.

PRESENTATION: 60/30 Tablets in HDPE Bottles alongwith packing inserts and packed in a unit carton.

STORAGE INSTRUCTIONS:
Store below 30ºC. Protect from light.
KEEP OUT OF REACH OF CHILDREN

MARKETED BY:

APRAZER

APRAZER Healthcare Pvt Ltd.
B-256 ,2nd. Floor, Naraina Phase -1,
New Delhi-110028, India
Web: www.aprazerhealthcare.com
TM-Trademark Under Registration