For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

ZULAMIVUDINE TABLET 150 MG

(Lamivudine Tablet 150mg)

COMPOSITION:

Each film coated tablet contains:

Lamivudine USP……..150 mg

PRODUCT DESCRIPTION:

White coloured capsule shaped, biconvex film coated tablet, having score on one side and 'ML 1' debossed on the other side of the tablet.

PHARMACOLOGICAL CLASSIFICATION:

Therapeutic Code: ***ATC code :*** **J05 A F05**

Pharmacotherapeutic group : Nucleoside analogue

PHARMACOKINETICS:

Lamivudine is a synthetic nucleoside analogue. Intracellularly, lamivudine is phosphorylated to its active ′5 -triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is the inhibition of HIV-1 reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue into viral DNA. 3TC-TP is a weak inhibitor of mammalian DNA polymerases α, β, and γ.

PHARMACOKINETICS:

Absorption:

Lamivudine was rapidly absorbed after oral administration in HIV-1-infected patients. The peak serum lamivudine concentration (Cmax) was 1.5 ± 0.5 mcg/mL (mean ± SD). The accumulation ratio of lamivudine in HIV-1-positive asymptomatic adults with normal renal function was 1.50

Distribution:

Binding of lamivudine to human plasma proteins is low (< 36%). In vitro studies showed that over the concentration range of 0.1 to 100 mcg/mL, the amount of lamivudine associated with erythrocytes ranged from 53% to 57% and was independent of concentration.

Metabolism:

Metabolism of lamivudine is a minor route of elimination. Metabolite of lamivudine is the trans-sulfoxide metabolite. Within 12 hours after a single oral dose of lamivudine in HIV-1-

infected adults, 5.2% ± 1.4% (mean ± SD) of the dose was excreted as the trans-sulfoxide metabolite in the urine. Serum concentrations of this metabolite have not been determined.

Excretion:

The majority of lamivudine is eliminated unchanged in urine by active organic cationic secretion. In healthy subjects given a single 300-mg oral dose of lamivudine, renal clearance was 199.7 ± 56.9 mL/min.

INDICATIONS:

Lamivudine, in combination with other anti-retroviral agents, is indicated for the treatment of HIV infected adults and children.

CONTRAINDICATIONS:

Lamivudine tablets are contraindicated in patients with known hypersensitivity to Lamivudine or to any of the components of the products.

RECOMMENDED DOSAGE:

Lamivudine therapy should be initiated by a physician experienced in the management of HIV infection.

Lamivudine can be taken with or without food.

To ensure administration of the entire dose, the tablet(s) should ideally be swallowed without crushing. For patients who are unable to swallow tablets, other approved dosage forms and strengths of Lamivudine should be used in such cases.

-Adults and adolescents weighing at least 30 kg

The recommended dose of *Lamivudine* is 300 mg daily.

This may be administered as 150 mg twice daily or 300 mg once daily.

·Children aged more than three months and weighing less than 30 kg

children weighing between 21 kg to 30 kg:-

The recommended oral dose of *Lamivudine 150mg Tablet* is 75mg taken in the morning and 150 mg (one whole tablet) taken in the evening.

-Children weighing 14 to 21 kg:-

The recommended oral dose of *Lamivudine 150mg Tablet* is 75 mg taken twice daily.

· **Children less than three months**

The limited data available are insufficient to propose specific dosage recommendations.

· **Elderly**

No specific data are available; however, special care is advised in this age group due to age associated changes such as the decrease in renal function and alteration of haematological parameters.

·**Renal impairment**

Lamivudine plasma concentrations (AUC) are increased in patients with moderate to severe renal impairment due to decreased clearance. The dosage should therefore be reduced for patients with a creatinine clearance of less than 50 ml/min as shown in the table below. The same percentage reduction in dose applies for paediatric patients with renal impairment. When doses below 150 mg are required, other approved dosage forms and strengths of Lamivudine should be used in such cases.

Dosing Recommendations - Adults and adolescents weighing at least 30 kg:

Creatinine clearance (ml/min)	**First Dose**	**Maintenance Dose**
30 to less than 50	150 mg	150 mg once daily
15 to less than 30	150 mg	100 mg once daily
5 to less than 15	150 mg	50 mg once daily
less than 5	50 mg	25 mg once daily

Dosing Recommendations - Children aged more than 3 months and weighing less than 30 kg

Creatinine clearance (ml/min)	**First Dose**	**Maintenance Dose**
30 to less than 50	4 mg/kg	4 mg/kg once daily
15 to less than 30	4 mg/kg	2.6 mg/kg once daily
5 to less than 15	4 mg/kg	1.3 mg/kg once daily
less than 5	1.3 mg/kg	0.7 mg/kg once daily

- **Hepatic impairment**

No dose adjustment is necessary in patients with moderate or severe hepatic impairment unless accompanied by renal impairment.

- **Route of Administration:**

Oral

DRUG INTERACTIONS:

The likelihood of interactions is low due to limited metabolism and plasma protein binding and almost complete renal elimination of unchanged lamivudine.

Lamivudine is predominantly eliminated by active organic cationic secretion. The possibility of interactions with other medicinal products administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system e.g. trimethoprim. Other active substances (e.g. ranitidine, cimetidine) are eliminated only in part by this mechanism and were shown not to interact with lamivudine.

Active substances shown to be predominately excreted either via the active organic anionic pathway, or by glomerular filtration are unlikely to yield clinically significant interactions with lamivudine.

Zidovudine: A modest increase in Cmax was observed for zidovudine when administered with lamivudine, however overall exposure (AUC) was not significantly altered. Zidovudine had no effect on the pharmacokinetics of lamivudine.

Trimethoprim/ sulphamethoxazo/e: Administration of trimethoprim/ sulphamethoxazole 160mg/800 mg (co-trimoxazole) causes a 40% increase in lamivudine exposure because of the trimethoprim component. However, unless the patient has renal impairment, no dosage adjustment of *lamivudine* is necessary.

Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulphamethoxalole. The effect of co-administration of *lamivudine* with higher doses of co-trimoxazole for the treatment of *Pneumocystis* jiroveci *(P.carinii)* pneumonia and toxoplasmosis has not been studied.

Zalcitabine: 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 zaicitabine.

ADVERSE REACTIONS:

Blood and lymphatic system disorders
Uncommon : Neutropenia, anaemia, thrombocytopenia.
Very rare : Pure red cell aplasia
Metabolism and nutrition disorders
Common : Hyperlactataemia.
Rare : Lactic acidosis
Redistribution/accumulation of body fat. The incidence of this event is dependent on multiple factors including the particular antiretroviral drug combination.
Nervous system disorders
Common : Headache.
Very rare : Paraesthesia. Peripheral neuropathy has been reported although a causal relationship to treatment is uncertain.
Gastrointestinal disorders
Common : Nausea, vomiting, upper abdominal pain, diarrhoea.
Rare : Pancreatitis, although a causal relationship to treatment is uncertain. Rises in serum amylase.
Hepatobiliary disorders
Uncommon : Transient rises in liver enzymes (AST, ALT).
Skin and subcutaneous tissue disorders
Common : Rash, alopecia.
Musculoskeletal and connective tissue disorders
Common : Arthralgia, muscle disorders.
Rare : Rhabdomyolysis.
General disorders and administration site conditions
Common : Fatigue, malaise, fever.

WARNINGS & PRECAUTION:

Lamivudine is not recommended for use as monotherapy.

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 receiving Lamivudine or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close clinical observation by physicians experienced in the treatment of patients with associated HIV diseases.

• **Renal impairment**

Lamivudine plasma concentrations (AUC) are increased in patients with moderate to severe renal impairment due to decreased clearance. The dose should therefore be adjusted.

• **Pancreatitis**

Pancreatitis has been observed in some patients receiving Lamivudine However it is unclear whether this was due to treatment with the medicinal product or to the 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**

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues either alone or in combination, including lamivudine. A majority of these cases have been in women.

Clinical features which may be indicative of the development of lactic acidosis include generalised weakness, anorexia, and sudden unexplained weight loss, gastrointestinal symptoms and respiratory symptoms (dyspnoea and tachypnoea).

Caution should be exercised when administering lamivudine to any patient, and particularly to those 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 (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

• **Fat redistribution**

Redistribution/ accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, elevated serum lipid and blood glucose levels have been observed either separately or together in some patients receiving combination antiretroviral therapy.

Whilst all members of the PI and NRTI classes of medicinal products have been associated with one or more of these specific adverse events, linked to a general syndrome commonly referred to as lipodystrophy, data indicate that there are differences in the risk between individual members of the respective therapeutic classes.

In addition, the lipodystrophy syndrome has a multi-factorial aetiology; with for example HIV disease status, older age and duration of antiretroviral treatment all playing important, possibly synergistic roles.

The long-term consequences of these events are currently unknown.

Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of serum lipids and blood glucose, lipid disorders should be managed as clinically appropriate.

• **Immune Reconstitution Syndrome**

In HIV-infected patients with severe immune deficiency at the time of initiation of anti-retroviral therapy (ART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of ART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and *Pneumocystis jiroveci (P. carinii)* pneumonia. Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary.

• **Patients co-infected with Hepatitis B virus**

Marketed use of lamivudine have shown that some patients with chronic hepatitis B virus (HBV) disease may experience clinical or laboratory evidence of recurrent hepatitis upon discontinuation of lamivudine, which may have more severe consequences in patients with decompensated liver disease. If lamivudine is discontinued in a patient with HIV and HBV coinfection, periodic monitoring of both liver function tests and markers of HBV replication should be considered.

Effects on Ability t o Drive and Use Machines

There have been no studies to investigate the effect of *Lamivudine on* driving performance or the ability to operate machinery. Further, a detrimental effect on such activities cannot be predicted from the pharmacology of lamivudine.

Nevertheless, the clinical status of the patient and the adverse event profile of lamivudine should be borne in mind when considering the patient's ability to drive or operate machinery.

Pregnancy:

Pregnancy Category C: There are no adequate and well-controlled studies of lamivudine tablet in pregnant women. Lamivudine tablet should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers:

Because of the potential for serious adverse reactions in nursing infants and HIV-1 transmission, mothers should be instructed not to breastfeed if they are receiving lamivudine tablet.

OVERDOSAGE:

Limited data are available on the consequences of ingestion of acute overdoses in humans.No fatalities occurred and the patients recovered. No specific signs or symptoms have been identified following such overdose.

If overdosage occurs, the patient should be monitored and standard supportive treatment to be applied as required.

STORAGE:

Store below 30°C in a dry place and protect from light.

Keep out of reach of children.

SHELF LIFE: 36 Months.

PRESENTATION:

60 tablets in a HDPE container which is then packed in a carton along with pack insert.

For further information please consult your physician or pharmacist

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