VALFIX FILM COATED TABLET 100MG

Ingredient(s):
Each tablet contains:
Lamivudine ..... 100 mg

Pharmacology (Summary of Pharmacodynamic and Pharmacokinetic):
Pharmacodynamic:
Lamivudine is an antiviral agent which is highly active against hepatitis B virus (HBV) in all cell lines tested and in experimentally infected animals.
Lamivudine is metabolised by both infected and uninfected cells to the triphosphate (TP) derivative which is the active form of the parent compound. The intracellular half-life of the triphosphate in hepatocytes is 17-19 hrs *in vitro*. Lamivudine-TP acts as a substrate for the HBV viral polymerase. The formation of further viral DNA is blocked by incorporation of lamivudine-TP into the chain and subsequent chain termination.
Lamivudine-TP does not interfere with normal cellular deoxynucleotide metabolism. It is also only a weak inhibitor of mammalian DNA polymerases α and β. Furthermore, lamivudine-TP has little effect on mammalian cell DNA content.
In assays relating to potential drug effects on mitochondrial structure and DNA content and function, lamivudine lacked appreciable toxic effects. It has a very low potential to decrease mitochondrial DNA content, is not permanently incorporated into mitochondrial DNA and does not act as an inhibitor of mitochondrial DNA polymerase γ.

Pharmacokinetic:
Absorption
Lamivudine is well absorbed from the gastrointestinal tract, and the bioavailability of oral lamivudine in adults is normally between 80-85%. Following oral administration, the mean time (tmax) to maximal serum concentrations (Cmax) is about an hour. At therapeutic dose levels ie. 100mg once daily, Cmax is in the order of 1.1-1.5 mcg/ml and trough levels were 0.015-0.02mcg/ml.
Co-administration of lamivudine with food resulted in a delay of tmax and a lower Cmax (decreased by up to 47%). However, the extent (based on the AUC) of lamivudine absorbed was not influenced, therefore lamivudine can be administrated with or without food.

Distribution
From IV studies, the mean volume of distribution is 1.3L/kg.
Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays low plasma protein-binding to albumin.
Limited data shows lamivudine penetrates the central nervous system and reaches the cerebrospinal fluid (CSF). The mean lamivudine CSF/serum concentration ratio 2-4 hrs after oral administration was approximately 0.12.

Metabolism
Lamivudine is predominantly cleared by renal excretion of unchanged drug. The likelihood of metabolic drug interactions with lamivudine is low due to the small (5-10%) extent of hepatic metabolism and the low plasma protein-binding.

Elimination
The mean systemic clearance of lamivudine is approximately 0.3L/hr/kg. The observed elimination half-life is 5-7 hrs. The majority of lamivudine is excreted unchanged in the urine via glomerular filtration and active secretion (organic cationic transport system).
Renal clearance accounts for about 70% of lamivudine elimination.

Special populations
Studies in patients with renal impairment show lamivudine elimination is affected by renal dysfunction. Dose reduction in patients with a creatinine clearance of <50mL/min is necessary.
A study in hepatically impaired patients (non-HIV and non-HBV infected) showed lamivudine is well tolerated in this patient group with no changes in laboratory parameter or the adverse event profile of lamivudine. The pharmacokinetics of lamivudine are unaffected by hepatic impairment.
Limited data in patients undergoing liver transplantation show that impairment of hepatic function does not impact significantly on the pharmacokinetics of lamivudine unless accompanied by renal dysfunction.
In elderly patients, the pharmacokinetics profile of lamivudine suggests that normal ageing with accompanying renal decline has no clinically significant effect on lamivudine exposure, except in patients with creatinine clearance of <50mL/min.
Following oral administration, lamivudine pharmacokinetics in late pregnancy were similar to non-pregnant adults.

Indication(s):
For treatment of patients ≥ 16 years of age with chronic hepatitis B and evidence of hepatitis B virus (HBV) replication.

Dosage and Administration
100mg once daily to be taken with or without food.
Patient compliance should be monitored while taking lamivudine. Discontinuation may be considered in immunocompetent patients when HBeAg and/or HBsAg seroconversion occur. Discontinuation may also be considered when loss of efficacy occurs, as indicated by recurrent signs of hepatitis.
After treatment discontinuation, patients should be periodically monitored for evidence of recurrent hepatitis.
Discontinuation of treatment is not recommended in patients with decompensated liver disease. There are limited data regarding the maintenance of long-term seroconversion after stopping treatment with lamivudine.

Renal impairment
Lamivudine serum concentrations (AUC) are increased in patients with moderate to severe renal impairment due to decreased renal clearance. The dosage should therefore be reduced in patients with creatinine clearance <50ml/min.
Data available in patients undergoing intermittent haemodialysis (≤4 hrs dialysis 2-3 times weekly), indicate that following the initial dosage reduction of lamivudine to correct for the patient's creatinine clearance, no further dosage adjustments are required while undergoing dialysis.

Hepatic impairment
Data obtained in patients with hepatic impairment, including those with end-stage liver disease awaiting transplant, show that lamivudine pharmacokinetics are not significantly affected by hepatic dysfunction. Based on these data, no dose adjustment is necessary in patients with hepatic impairment unless accompanied by renal impairment.

Mode of Administration
To be taken orally with or without food.

Contraindication
Patients with known hypersensitivity to lamivudine or to any ingredient of this product.

Precaution(s) / Warning(s):
1. During treatment, patients should be monitored regularly by a physician experienced in the management of chronic hepatitis B.
2. If this product is discontinued or there is a loss of efficacy, some patients may experience clinical or laboratory evidence of recurrent hepatitis. Exacerbation of hepatitis has primarily been detected by serum ALT elevations, in addition to the re-emergence of HBV DNA.
3. If this product is discontinued, patients should be periodically monitored both clinically and by assessment of serum liver function tests (ALT and bilirubin levels), for at least 4 months for evidence of recurrent hepatitis; patients should then be followed as clinically indicated. For patients who develop evidence of recurrent post-treatment hepatitis, there are insufficient data on the benefits of re-initiation of lamivudine treatment.
4. In patients with moderate to severe renal impairment, serum lamivudine concentrations (AUC) are increased due to decreased renal clearance, therefore, the dose should be reduced in patients with creatinine clearance <50 ml/min.
5. Transplantation recipients and patients with advanced liver disease are at greater risk from active viral replication. Due to marginal liver function in these patients, hepatitis reactivation at discontinuation of lamivudine or loss of efficacy during treatment may induce severe and even fatal decompensation. It is

recommended that these patients are monitored for parameters associated with hepatitis B, for liver and renal function, and for antiviral response during treatment. If treatment is discontinued for any reason, it is recommended that these patients are monitored for at least 6 months after cessation of treatment. Patients experiencing signs of hepatic insufficiency during or post-treatment should be monitored frequently, as appropriate.

6. There are limited data on the use of lamivudine in patients receiving concurrent immunosuppressive regiments, including cancer chemotherapy.
7. HBV viral subpopulations (YMDD variant HBV) with reduced susceptibility to lamivudine have been identified during extended therapy. In a minority of cases, this variant can lead to recurrent hepatitis.
8. For the treatment of patients who are co-infected with HIV and are currently receiving or are planning to receive an antiretroviral treatment regimen including lamivudine, the dose of lamivudine usually prescribed for HIV infection should be maintained.
9. There is no information available on maternal-foetal transmission of hepatitis B virus in pregnant women receiving treatment with this product. The standard recommended procedures for hepatitis B virus immunization in infants should be followed.
10. Patients should be advised that therapy with this product have not been proven to reduce the risk of transmission of hepatitis B virus to others and therefore, appropriate precaution should still be taken.
11. Effects on the ability to drive or operate machinery: There have been no studies to investigate the effect of lamivudine on driving performance or the ability to operate machinery. Furthermore, a detrimental effect on such activities would not be predicted from the pharmacology of lamivudine.

Interaction with Other Medicaments:
The likelihood of metabolic interactions is low due to limited metabolism and plasma protein-binding and almost complete renal elimination of unchanged drug.
Lamivudine is predominantly eliminated by active organic cationic secretion. The possibility of interactions with other drugs administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system eg. trimethoprim. Other drugs (eg. ranitidine, cimetidine) are eliminated only in part by this mechanism and were shown not to interact with lamivudine.
Drugs shown to be predominantly excreted either via the active organic anionic pathway or by glomerular filtration are unlikely to yield clinically significant interactions with lamivudine.
Lamivudine has no pharmacokinetic interaction with α-interferon when the 2 drugs are concurrently administered. There were no observed clinically significant adverse interactions in patients taking this product with commonly used immunosuppressant drugs (eg. cyclosporine A). However, formal interaction studies have not been performed.
Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the 2 medicinal products are used concurrently. This product is therefore not recommended to be used in combination with zalcitabine.
Emtricitabine
Due to similarities, lamivudine should not be administered concomitantly with other cytidine analogues, such as emtricitabine. Moreover, lamivudine should not be taken with any other medicinal products containing lamivudine.

Pregnancy and Lactation:
Use in pregnancy
Studies in humans have confirmed that Lamivudine crosses the placenta. Lamivudine concentrations in infant serum at birth were similar to those in maternal and cord serum at delivery.

Use in pregnancy should be considered only if the benefit outweighs the risk. Although the results of animal studies are not always predictive of human response, the findings in the rabbit suggest a potential risk of early embryonic loss.

Consequently, Lamivudine administration is not recommended during the first three months of pregnancy.
For patients who are being treated with Lamivudine and subsequently become pregnant consideration should be given to the possibility of a recurrence of hepatitis on discontinuation of Lamivudine.

Lactation
Lamivudine should only be used in a nursing mother if the expected benefit justifies the potential risk to the infant. A decision must be made whether to discontinue breast feeding or to discontinue/abstain from Lamivudine therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Side Effect(s) / Adverse Reaction(s):
The most common adverse events reported are malaise and fatigue, respiratory tract infections, headache, abdominal discomfort and pain, nausea, vomiting and diarrhoea.
Hepatobiliary disorders: Elevation of ALT.
Musculoskeletal, connective tissue and bone disorders: Elevation of CPK, muscle disorders, including myalgia and cramps.
Blood and lymphatic system disorders: Thrombocytopenia
In patients with HIV infection, cases of pancreatitis and peripheral neuropathy (or paresthesia) have been reported, although no relationship to treatment with lamivudine has been clearly established.
Cases of lactic acidosis, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of nucleoside analogue combination therapy in patients with HIV. There have been occasional reports of these adverse events in hepatitis B patients with decompensated liver disease.

Symptoms and Treatment for Overdosage, and Antidote(s):
Administration of lamivudine at very high dose levels in acute animal studies did not result in any organ toxicity. 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 overdose occurs, the patient should be monitored, and standard supportive treatment applied as required. Since lamivudine is dialysable, continuous haemodialysis could be used in the treatment of overdose, although this has not been studied.

Shelf-Life:
3 years from the date of manufacture.

Storage Condition(s):
Store at temperature below 30°C.

Product Description:
An orange-brown elliptical tablet, one side impressed with 'BM' " BM ( ) "

Dosage Forms and Packaging available:
Blister packing of 10's x 3, 10's x 6, 10's x 10, 10's x 50 and 10's x 100.

Y. S. P. ®

Manufacturer and Product Registration Holder :
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