Axcel®

LAMIVUDINE-100mg
TABLET

MAL12060008AZ

COMPOSITION:
Each tablet contains
Lamivudine 100mg

PRESENTATION:
Butterscotch coloured, oval biconvex, film coated tablets.

INDICATION:
Indicated for the treatment of patients ≥ 16 years of age with chronic hepatitis B and evidence of hepatitis B virus (HBV) replication.

PHARMACOLOGY:
Mechanism of Action:
Axcel Lamivudine Tablet is an antiviral agent which is highly active against hepatitis B virus 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 to 19 hours 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.

Pharmacokinetics:
Absorption:
Lamivudine is well absorbed from the gastrointestinal tract, and the bioavailability of oral Lamivudine in adults is normally between 80% and 85%. Following oral administration, the mean time (t_{max}) to maximal serum concentrations (C_{max}) is about an hour. At the therapeutic dose levels i.e. 100mg once daily, C_{max} is in the order of 1.1-1.5µg/ml and through levels were 0.015-0.020µg/ml. Co-administration of Axcel Lamivudine Tablet with food resulted in a delay of t_{max} and lower C_{max} (decreased by up to 47%). However, the extent (based on the AUC) of Lamivudine absorbed was not influenced, therefore Axcel Lamivudine Tablet can be administered with or without food.

Distribution:
From intravenous 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 hours after oral administration was approximately 0.12.

Metabolism:
Lamivudine is predominately 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.

Effect of other agents on the pharmacokinetics of lamivudine:
Lamivudine is a substrate of MATE1, MATE2-K and OCT2 in vitro. Trimethoprim (an inhibitor of these drug transporters) when given in combination with sulphamethoxazole, has been shown to increase lamivudine plasma concentrations (See Drug Interactions). Lamivudine is a substrate of the hepatic uptake transporter OCT1. As hepatic elimination plays a minor role in the clearance of lamivudine, drug interactions due to inhibition of OCT1 are unlikely to be of clinical significance. Lamivudine is an in vitro substrate of Pgp and BCRP, however due to its high bioavailability it is unlikely that these transporters play a significant role in the absorption of lamivudine. Therefore, co-administration of drugs that are inhibitors of these efflux transporters is unlikely to affect the disposition and elimination of lamivudine.

Effect of lamivudine on the pharmacokinetics of other agents:
In vitro, lamivudine demonstrates no or weak inhibition of the drug transporters organic anion transporter 1B1 (OATP1B1), OATP1B3, breast cancer resistance protein (BCRP) or Pglycoprotein (Pgp), multidrug and toxin extrusion protein 1 (MATE1), MATE2-K or organic cation transporter 3 (OCT3). Lamivudine is therefore not expected to affect the plasma concentrations of drugs that are substrates of these drug transporters. Lamivudine is an inhibitor of OCT1 and OCT2 in vitro with IC50 values of 17 and 33 uM, respectively, however lamivudine has low potential to affect the plasma concentrations of OCT1 and OCT2 substrates at therapeutic drug exposures (up to 300 mg which is three times higher than the recommended maximum dose for HBV).

Elimination:
The mean systemic clearance of lamivudine is approximately 0.3 L/h/kg. The observed half- life of elimination is 18 to 19 hours. 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 patient populations:
Elderly
In elderly patients the pharmacokinetic 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 less than 50 mL/min (see Dosage and Administration).

Renal impairment
Studies in patients with renal impairment show lamivudine elimination is affected by renal dysfunction. Dose reduction in patients with a creatinine clearance of less than 50 mL/min is necessary (see Dosage and Administration).

Hepatic impairment
A study in hepatically impaired patients (non-HIV and non-HBV infected) showed Axcel Lamivudine Tablet is well tolerated in this patient group with no changes in laboratory parameters or the adverse event profile of Axcel Lamivudine Tablet. 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.

Pregnancy
Following oral administration, lamivudine pharmacokinetics in late pregnancy were similar to non-pregnant adults. Lamivudine concentrations in infant serum at birth were similar to those in maternal and cord serum at delivery.

DOSAGE AND ADMINISTRATION:
For oral administration only; may be taken with or without food. The recommended dosage of Axcel Lamivudine Tablet is 100 mg once daily. Patient compliance should be monitored while on Axcel Lamivudine Tablet therapy. Discontinuation of Axcel Lamivudine Tablet may be considered in immunocompetent patients when HBeAg and/or HBsAg seroconversion occurs. Discontinuation may also be considered when loss of efficacy occurs, as indicated by recurrent signs of hepatitis. If Axcel Lamivudine Tablet is discontinued, patients should be periodically monitored for evidence of recurrent hepatitis (see Warnings and Precautions). Discontinuation of treatment is not recommended in patients with decompensated liver disease. There are limited data regarding the maintenance of seroconversion long term after stopping treatment with Axcel Lamivudine Tablet. Axcel Lamivudine Tablet should be used in accordance with available official recommendations.

Population:
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 for patients with a creatinine clearance of <50ml/minute. Data available in patients undergoing intermittent haemodialysis (less than or equal to 4 hours dialysis 2 to 3 times weekly), indicate that following the initial dosage reduction of Axcel Lamivudine Tablet 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 Axcel Lamivudine Tablet 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.

CONTRAINDICATION:
Axcel Lamivudine Tablet is contraindicated in patients with known hypersensitivity to Lamivudine or to any ingredient of the preparation.

WARNING AND PRECAUTIONS:
Initiation of Axcel Lamivudine Tablet treatment should only be considered when the use of an alternative antiviral agent with a higher genetic barrier to resistance is not available or appropriate. During initiation and maintenance of treatment patients should be monitored regularly by a physician experienced in the management of chronic hepatitis B. If Axcel Lamivudine Tablet 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. Most events appear to have been self-limited. Fatalities are very rare and the causal relationship to discontinuation of Axcel Lamivudine Tablet treatment is unknown. If Axcel Lamivudine Tablet is discontinued, patients should be periodically monitored both clinically and by assessment of serum liver function tests (ALT and bilirubin levels), for at least four months for evidence of recurrent hepatitis; patients should then be followed as clinically indicated. For patients who develop evidence of recurrent hepatitis post-treatment, there are insufficient data on the benefits of re-initiation of Axcel Lamivudine Tablet treatment. 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 for patients with a creatinine clearance of less than 50 mL/minute (see Dosage and Administration). 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 Axcel Lamivudine Tablet 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 post cessation of treatment. Patients experiencing signs of hepatic insufficiency during or post-treatment should be monitored frequently, as appropriate. There are limited data on the use of Axcel Lamivudine Tablet in patients receiving concurrent immunosuppressive regimes, including cancer chemotherapy. In HBeAg positive or negative patients, the development of YMDD (tyrosine-methionineaspartate-aspartate) mutant HBV may result in a diminished therapeutic response to lamivudine, indicated by a rise in HBV DNA and ALT from previous on-treatment levels. In order to reduce the risk of resistance in patients receiving lamivudine monotherapy, a switch to or addition of an alternative agent without cross-resistance to lamivudine should be considered if serum HBV DNA remains detectable at or beyond 24 weeks of treatment. For the treatment of patients who are coinfected with HIV and are currently receiving or are planning to receive an antiretroviral combination regimen including lamivudine, the dose of lamivudine usually prescribed for HIV infection should be maintained. The dose of lamivudine used for the treatment of HBV is not appropriate for patients who acquire HIV or are co-infected with HBV and HIV. If a patient with unrecognised or untreated HIV infection is prescribed the dose of lamivudine recommended for the treatment of HBV, rapid emergence of HIV resistance and a limitation of treatment options is likely to result because of the subtherapeutic dose and the inappropriate use of monotherapy for HIV treatment. HIV counselling and testing should be offered to all patients before beginning treatment with Axcel Lamivudine Tablet for HBV and periodically during treatment. There is limited information available on maternal-foetal transmission of hepatitis B virus in pregnant women receiving treatment with Axcel Lamivudine Tablet. The standard recommended procedures for hepatitis B virus immunisation in infants should be followed. Patients should be advised that therapy with Axcel Lamivudine Tablet has not been proven to reduce the risk of transmission of hepatitis B virus to others and therefore, appropriate precautions should still be taken.

Effects on Ability to Drive and Use Machines:
There have been no studies to investigate the effect of Axcel Lamivudine Tablet on driving performance or the ability to operate machinery. Further a detrimental effect on such activities would not be predicted from the pharmacology of the drug.

Fertility:
Reproductive studies in animals have shown no effect on male or female fertility.

Pregnancy:
Lamivudine has been evaluated in the Antiretroviral Pregnancy

Registry in over 11,000 women during pregnancy and postpartum. Less than 1% of these women have been treated for HBV, whereas the majority was treated for HIV at higher doses and with other concomitant HIV medications. Available human data from the Antiretroviral Pregnancy Registry do not show an increased risk of major birth defects for lamivudine compared to the background rate. However, there are no adequate and well-controlled trials in pregnant women and the safe use of lamivudine in human pregnancy has not been established. Studies in humans have confirmed that Axcel Lamivudine Tablet crosses the placenta. 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, there was no evidence of teratogenicity in animals but, findings in rabbits suggest a potential risk of early embryonic loss that was not observed in the rat. For patients who are being treated with Axcel Lamivudine Tablet and subsequently become pregnant consideration should be given to the possibility of a recurrence of hepatitis on discontinuation of Axcel Lamivudine Tablet (see Warnings and Precautions).

Lactation:
Following repeat oral administration of either 150 mg or 300 mg lamivudine twice daily, lamivudine was excreted in human breast milk (0.5 to 8.2 micrograms/mL) at similar concentrations to those found in serum. In other studies following repeat oral administration of 150 mg lamivudine twice daily the breast milk: maternal plasma ratio ranged between 0.6 and 3.3. Lamivudine median infant serum concentrations ranged between 18 and 28 ng/mL and were not detectable in one of the studies (assay sensitivity 7 ng/mL). The clinical relevance of this finding is unknown. Data from animal studies in which neonatal rats received Axcel Lamivudine Tablet at much higher concentrations via maternal milk suggest that the concentrations of lamivudine in human breast milk are unlikely to produce toxicity in breast fed infants. Axcel Lamivudine Tablet 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 Axcel Lamivudine Tablet therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

SIDE EFFECTS:
The most common adverse events reported were malaise and fatigue, respiratory tract infections, headache, abdominal discomfort and pain, nausea, vomiting and diarrhoea. Adverse reactions are listed below by system organ class and frequency. Frequency categories are only assigned to those adverse reactions considered to be at least possibly causally related to Lamivudine. Frequencies are defined as: very common (≥1/10), common (≥ 1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000) and very rare (<1/10,000).

Hepatobiliary disorders
Very common: Elevations of ALT
Elevations in ALT were more common post-treatment in patients treated with Axcel Lamivudine Tablet than placebo. In controlled trials in patients with compensated liver disease, however, there was no appreciable difference post treatment in clinically severe ALT elevations associated with bilirubin elevations and / or signs of hepatic insufficiency, between Axcel Lamivudine Tablet and placebo treated patients. The relationship of these recurrent hepatitis events to Axcel Lamivudine Tablet treatment or to the previous underlying disease is uncertain (see Warnings and Precautions).

Skin and subcutaneous tissue disorder
Common: Rash

Musculoskeletal and connective tissue disorders
Common: Elevations of CPK
Post Marketing Data:
In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of Axcel Lamivudine Tablet.

Blood and lymphatic system disorders
Very rare: Thrombocytopenia.

Musculoskeletal and connective tissue disorders
Common: Muscle disorders, including myalgia and cramps.
Very rare: Rhabdomyolysis.

In patients with HIV infection, cases of pancreatitis and peripheral neuropathy (or paraesthesia) have been reported, although no relationship to treatment with lamivudine (EPIVIR) has been clearly established. In patients with chronic hepatitis B there was no observed difference in incidence of these events between placebo and Axcel Lamivudine Tablet treated patients. Cases of lactic acidosis, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of combination nucleoside analogue therapy in patients with HIV. There have been occasional reports of these adverse events in hepatitis B patients with decompensated liver disease, however there is no evidence that these events were related to treatment with Lamivudine.

DRUG INTERACTION:
The likelihood of metabolic interactions is low due to limited metabolism and plasma protein binding and almost complete renal elimination of unchanged drug. Axcel Lamivudine Tablet 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 e.g. trimethoprim. Other drugs (e.g. ranitidine, cimetidine) are eliminated only in part by this mechanism and were shown not to interact with Axcel Lamivudine Tablet. Drugs shown to be predominately excreted either via the active organic anionic pathway, or by glomerular filtration are unlikely to yield clinically significant interactions with Axcel Lamivudine Tablet.

Interactions relevant to lamivudine
Trimethoprim/ sulphamethoxazole:
Administration of trimethoprim/ sulphamethoxazole 160 mg/800 mg increased Axcel Lamivudine Tablet exposure by about 40%. Axcel Lamivudine Tablet had no effect on the pharmacokinetics of trimethoprim or sulphamethoxazole. However, unless the patient has renal impairment, no dosage adjustment of Axcel Lamivudine Tablet is necessary.

Zidovudine:
A modest increase in Cmax (28%) was observed for zidovudine when administered with Axcel Lamivudine Tablet, however overall exposure (AUC) was not significantly altered. Zidovudine had no effect on the pharmacokinetics of Axcel Lamivudine Tablet (see Pharmacokinetics).

Emtricitabine:
Axcel Lamivudine Tablet may inhibit the intracellular phosphorylation of emtricitabine when the two medicinal products are used concurrently. Axcel Lamivudine Tablet is not recommended for use in combination with emtricitabine.

Sorbitol:
Coadministration of sorbitol solution (3.2 g, 10.2 g, 13.4 g) with a single 300 mg dose (Adult HIV daily dose) of lamivudine oral solution resulted in dose-dependent decreases of 14%, 32%, and 36% in lamivudine exposure (AUC⊠) and 28%, 52%, and 55% in the Cmax of lamivudine in adults. When possible, avoid use of Axcel Lamivudine Tablet with sorbitol-containing medicines or consider more frequent monitoring of HBV viral load when chronic coadministration cannot be avoided.

Alpha-interferon:
Axcel Lamivudine Tablet has no pharmacokinetic interaction with alpha-interferon when the two drugs are concurrently administered. There were no observed clinically significant adverse interactions in patients taking Lamivudine concurrently with commonly used immunosuppressant drugs (e.g. cyclosporin A). However, formal interaction studies have not been performed.

OVERDOSAGE AND TREATMENT :
No specific signs of symptoms have been identified following such overdose. If overdose occurs the patients 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 has not been studied.

STORAGE:
Store below 30^{o}C. Protect from light.

KEEP OUT OF REACH OF CHILDREN
JAUHI DARI KANAK-KANAK

PACK QUANTITIES:
Available in blister pack of 3 x 10's and 10 x 10's.

Further information can be obtained from pharmacist, physician or the manufacturer.

Product Registration Holder and Manufactured By :
Kotra Pharma (M) Sdn. Bhd. (90082-V)
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