ZEFFIX TABLETS AND ORAL SOLUTION

NAME OF THE DRUG:

Lamivudine

DESCRIPTION:

Chemically, lamivudine is the free base of (2R-cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one, and has the following structural formula:

![Structural formula of lamivudine](image)

The molecular formula of lamivudine is C$_8$H$_{11}$N$_3$O$_3$S and it has a relative molecular mass of 229.3.

Lamivudine is a white to off-white crystalline solid which is highly soluble in water.

CAS REGISTRY NUMBER: 134678-17-4

PHARMACOLOGY:

Pharmacodynamics

Lamivudine is an antiviral agent which is highly active against hepatitis B virus in virus-transfected human hepatoma cell lines and in experimentally infected animals.

Lamivudine is metabolised by both hepatitis B virus-transfected and non-transfected hepatoma cells to the triphosphate (TP) derivative which is the active form of the parent compound. The intracellular half life of the triphosphate in hepatoma cells is 17 – 19 hours in vitro. Lamivudine-TP acts as a substrate for the HBV viral polymerase. It is considered that 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 cellular deoxynucleotide metabolism. It is also a weak inhibitor of mammalian DNA polymerases alpha and beta. 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 gamma.

**Pharmacokinetics**

**Absorption:** Lamivudine is well absorbed from the gut, and the bioavailability of oral lamivudine in adults is normally between 80 and 85%. Following oral administration the mean time ($t_{\text{max}}$) to maximal serum concentrations ($C_{\text{max}}$) is about an hour. At therapeutic dose levels ie 100mg once daily, $C_{\text{max}}$ is in the order of 1-1.5 µg/mL and trough levels were 0.015 – 0.020 µg/mL.

The 100mg tablet was administered orally to 16 healthy subjects on two occasions, once in the fasted state and once with food (standard meal: 967 kcal; 67 grams fat, 33 grams protein, 58 grams carbohydrate). There was no significant difference in systemic exposure ($\text{AUC}_{\text{inf}}$) in the fed and fasted states. A reduction in $C_{\text{max}}$ (about 10%) and delay in $T_{\text{max}}$ (0.25hrs) with the ingestion of a high fat meal were not statistically or clinically significant.

**Distribution:** From intravenous studies, the mean volume of distribution is 1.3 L/kg. Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays low plasma protein binding to albumin.

Limited data show relatively low penetration of lamivudine into the central nervous system. The mean ratio CSF/serum lamivudine concentration 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 limited metabolism and plasma protein binding and almost complete renal clearance. An interaction with trimethoprim, a constituent of co-trimoxazole (trimethoprim with sulphamethoxazole) causes a 40% increase in lamivudine exposure at therapeutic doses.

**Elimination:** The mean systemic clearance of lamivudine is approximately 0.3 L/h/kg. The observed half-life of elimination is 5 to 7 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 populations:**

Lamivudine pharmacokinetics were evaluated in a 28-day dose-ranging study in 53 paediatric patients with chronic hepatitis B. Patients aged 2 to 12 years were randomised to receive lamivudine 0.35mg/kg twice daily, 3mg/kg once daily, 1.5mg/kg twice daily, or 4mg/kg twice daily. Patients aged 13 to 17 years received lamivudine 100mg once daily. Lamivudine was rapidly absorbed ($T_{\text{max}}$ 0.5 to 1 hour). In general, both $C_{\text{max}}$ and exposure ($\text{AUC}$) showed dose proportionality in the dose range studied. Weight-correct oral clearance was highest at age 2 and declined from 2 to 12 years, where values were similar to those seen in adults. A dose of 3mg/kg given once daily produced a steady-state lamivudine AUC (mean 5953 ng.h/mL +/- 1562 SD) similar to that associated with a dose of 100mg/day in adults.

Studies in patients with renal impairment show there is a linear relationship between lamivudine clearance and renal function. Dose reduction in patients with a creatinine clearance of <50mL/min is necessary (see DOSAGE AND ADMINISTRATION). A study in non-HIV and non-HBV infected hepatically impaired patients (n=16) showed lamivudine is well tolerated in this patient group with no changes in laboratory parameters or
the adverse event profile of lamivudine. The pharmacokinetics of lamivudine are unaffected by hepatic impairment. Limited data in patients undergoing liver transplantation (n=14), show that impairment of hepatic function does not impact significantly on the pharmacokinetics of lamivudine unless accompanied by renal dysfunction.

In elderly patients (n=6) 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 <50mL/min. (see DOSAGE AND ADMINISTRATION).

Following oral administration, lamivudine pharmacokinetics in late pregnancy were similar to non-pregnant adults.

Clinical Trials

ADULTS

The safety and efficacy of lamivudine were evaluated in five controlled studies. One of the studies (NUCB3014) was conducted in HBeAg negative/HBV DNA positive patients.

NUCA3010 was a randomised, double-blind comparison in 143 patients in the USA of lamivudine 100mg once daily versus placebo for 52 weeks followed by a 16 week no treatment period in treatment naïve patients. The primary endpoint was improvement in liver histology. After 52 weeks of treatment a significantly greater number of patients who received lamivudine demonstrated an improvement in necro-inflammatory score compared to placebo (53% lamivudine vs. 24% placebo; p<0.001). HBeAg seroconversion occurred significantly more frequently in lamivudine patients (17%) than in placebo treated patients (6%) (p<0.05). Significantly more lamivudine treated patients demonstrated a sustained HBV DNA response (defined as negative HBV DNA on two consecutive occasions without two consecutive positive values to end week 52) compared to placebo (44% vs. 16% respectively; p<0.001). Similarly, a significantly greater number of lamivudine treated patients (41%) demonstrated a sustained normalisation of ALT (defined as two consecutive ALT values <ULN maintained to week 52) compared to placebo (7%; p<0.001).

NUCB3009 was a randomised, double-blind comparison of lamivudine 25 mg daily versus lamivudine 100mg daily versus placebo for 52 weeks in 358 Asian patients. The primary endpoint was improvement in liver histology. After 52 weeks of treatment a significantly greater number of patients who received lamivudine 100mg demonstrated an improvement in necro-inflammatory score compared to placebo (56% lamivudine vs. 25% placebo; p<0.001). HBeAg seroconversion occurred significantly more frequently in lamivudine 100mg patients (16%) than in placebo treated patients (4%) (p<0.05). Significantly more lamivudine 100mg treated patients demonstrated a sustained HBV DNA response compared to placebo (57% vs. 3% respectively; p<0.001). Similarly, a significantly greater number of lamivudine 100mg treated patients (72%) demonstrated a sustained normalisation of ALT compared to placebo (24%; p<0.001).

NUCB3010 was a randomised, partially blind comparison in 230 predominantly Caucasian patients of lamivudine 100mg once daily for 52 weeks versus placebo once daily for 8 weeks followed by placebo once daily plus interferon alpha monotherapy (10MU subcutaneously three times weekly) for 16 weeks versus lamivudine 100mg once daily for 8 weeks followed by lamivudine 100mg once daily plus interferon alpha monotherapy (10MU subcutaneously three times weekly) for 16 weeks. The primary endpoint was HBeAg seroconversion with concomitant clearance of HBV DNA. There was no statistically significant difference in the rates of HBeAg seroconversion demonstrated by the three treatment groups (18% lamivudine, 19% interferon-alpha, 29% lamivudine plus interferon alpha). A greater proportion of patients in the lamivudine treated group demonstrated a sustained ALT normalisation than in the
interferon-alpha alone group (40% vs. 17% respectively; p<0.01) but there was no difference
between lamivudine and the combination group. The safety profile of lamivudine 100mg daily
alone was superior to the alpha interferon containing treatment regimens.

NUCB3018 was a randomised, double-blind, placebo controlled follow-on study of
NUCB3009. The primary endpoint was sustained suppression of HBV DNA. Fifty-two per
cent of patients receiving lamivudine for two years achieved a sustained suppression in HBV
DNA through to week 104 compared to 5% of patients who received lamivudine for one year
followed by placebo (p<0.001). Sustained ALT response was evident in 50% of patients after
104 weeks lamivudine compared to 8% in patients randomised to placebo after the first 52
weeks of lamivudine (p<0.001). HBeAg seroconversion was observed in 27% (25/93) of
patients.

NUCB3014 was a randomised, double-blind comparison of lamivudine 100mg once daily for
52 weeks versus placebo for 26 weeks (non-responders were withdrawn at week 26) in 125
predominantly Caucasian patients with HBeAg negative/HBV DNA positive chronic hepatitis
B. The primary endpoint was combined clearance of HBV DNA and ALT normalisation.
Sustained suppression of HBV DNA at 52 weeks occurred significantly more often in the
lamivudine group (71%) than in the placebo group (15%) (p<0.001) demonstrating that
lamivudine is effective at suppressing HBV replication in patients infected with pre-core
mutant HBV. Sustained normalisation of serum ALT occurred in a significantly greater
proportion of lamivudine treated patients (67%) compared to placebo (5%)(p<0.001).

In the analysis of NUCB3009 and NUCA3010 progression of fibrosis occurred in more
patients receiving placebo compared to patients receiving lamivudine 100mg (NUCB3009
15% vs 3%, p=0.009; NUCA3010 27% v 6%, p=0.004). However, given the slow progression
of fibrosis, the long-term clinical significance of these results is not known.

In patients who have not HBeAg seroconverted during treatment, discontinuation of Zeffix
results in a return of HBV replication with both HBV DNA and serum aminotransferases
returning towards pre-treatment levels within 2-6 months.

In small uncontrolled studies in patients with decompensated liver disease due to chronic
hepatitis B, lamivudine 100mg daily has been administered prior to, during and post liver
transplantation, to suppress existing or recurrent HBV. In some of these patients, lamivudine
100mg daily demonstrated HBV suppression and normalisation of serum aminotransferase.

HBV viral sub-populations with reduced susceptibility to lamivudine in vitro have been
identified. In the sensitive polymerase chain reaction (PCR) assay YMDD variant HBV was
detected in a minority of chronic hepatitis B patients who experience a return of detectable
serum HBV DNA levels whilst on lamivudine 100mg daily treatment. YMDD variant HBV was
detected in a minority of chronic hepatitis B patients without decompensated liver disease
in treated with lamivudine 100mg once daily for 52 weeks (16-32%). The incidence of YMDD
variant HBV detected by PCR increases with duration of treatment (42% at 2 years) and may
be influenced by the immune status of the patient. A higher proportion of immunosuppressed
patients had detectable YMDD variant HBV during treatment of hepatitis B recurrence
following liver transplantation.

Despite the emergence of YMDD mutant HBV, patients treated for one year had significantly
lower serum HBV DNA and ALT levels and improved liver histology compared to patients on
placebo. After 2 years of Zeffix treatment, patients with YMDD mutant HBV maintained lower
serum HBV DNA and ALT levels than their pre-treatment values. The adverse event profile is
similar for patients with or without YMDD mutant HBV.

Following the development of YMDD mutant HBV, the withdrawal of lamivudine 100mg daily
was followed by a re-emergence of wild-type HBV which is sensitive to lamivudine 100mg
(see PRECAUTIONS). Therefore, despite the development of YMDD mutants, continuation of lamivudine 100mg therapy will suppress residual wild-type HBV and may provide continued benefit in these patients. YMDD mutant HBV appears to be less replication competent in vitro and in vivo and therefore may be less virulent than wild-type HBV.

**Children and Adolescents:**

In a randomised, double blind, placebo controlled study of 286 patients aged 2 to 17 years with chronic hepatitis B who were HBsAg positive for at least 6 months, HBeAg positive, with detectable HBV DNA, ALT ≥ 1.3XULN and liver biopsy evidence of inflammation. Patients were randomised (2:1) to receive 52 weeks of lamivudine 3mg/kg once daily to a maximum of 100mg once daily or placebo.

Patients treated with lamivudine for one year had a significantly better complete virological response (loss of HBeAg and HBV DNA) compared with patients receiving placebo (23% [44/191] vs 13% [12/95] p=0.037) Normalisation of serum ALT was more frequent in patients treated with lamivudine compared with placebo (55% [100/183] vs 13% [11/88] p<0.001). In a stratified follow-on study for 6 months, complete virological response was maintained in 83% [33/40] of patients who had responded after one year of treatment with lamivudine and then stopped therapy.

Lamivudine treated patients who did not respond after one year continued treatment for a further 6 months resulting in an additional 10% (12/123) of patients achieving complete virological response and a cumulative complete virological response of 28% (45/163) over 18 months. The complete virological response rate in the last 6 months of treatment was consistent with the placebo response rate, a benefit from continuing treatment in children beyond 52 weeks has not been established.

The incidence of YMDD variant HBV was 18% (30/166) at week 52 and up to 45% (53/118) in patients treated continuously for 18 months. No HBeAg seroconversion was observed in patients with YMDD variant HBV.

**INDICATIONS:**

Zeffix (lamivudine) is indicated for the treatment of children (2 years and above), adolescent and adult patients with chronic hepatitis B and evidence of hepatitis B virus (HBV) replication.

This indication is based on changes in serological and histological markers in clinical studies of up to 2 years duration in adult patients with compensated liver disease and serological data up to 18 months in children and adolescents. Children and adolescents also require evidence of active hepatic inflammation. (see Clinical Trials).

The safety and efficacy of Zeffix (lamivudine) have not been established in patients with decompensated liver disease in placebo controlled studies. However, Zeffix (lamivudine) has been shown to reduce HBV DNA levels prior to and post liver transplantation.

**CONTRAINDICATIONS:**

Zeffix is contra-indicated in patients with known hypersensitivity to lamivudine or to any ingredient of the preparation.

**PRECAUTIONS:**
Patients should be monitored regularly during treatment by a physician experienced in the management of chronic hepatitis B.

There are limited data on the use of lamivudine in patients receiving concurrent immunosuppressive regimes, including cancer chemotherapy, and therefore close monitoring of this group is required.

Pancreatitis and Neuropathy:

In patients with HIV infection, cases of pancreatitis and peripheral neuropathy (or paraesthesia) have been reported although no relationship to treatment with lamivudine (3TC™) has been clearly established. In patients with chronic hepatitis B there was no observed difference in the incidence of these events between placebo and lamivudine 100mg daily treated patients.

Lactic Acidosis and severe hepatomegaly:

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. A majority of these cases have been in women. Obesity and prolonged exposure nucleoside may be risk factors.

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.

Particular caution should be exercised when administering Zeffix to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with Zeffix should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Renal Impairment:

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 < 50 mL/minute. (see DOSAGE AND ADMINISTRATION).

Cirrhotic liver disease/Hepatitis B virus:

If Zeffix 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. Most events appear to have been self-limited. Fatalities are very rare and the causal relationship to discontinuation of lamivudine treatment is unknown.

If lamivudine 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 re-initiation of lamivudine treatment.
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 post cessation of treatment. Patients experiencing signs of hepatic insufficiency during or post-treatment should be monitored frequently, as appropriate.

HBV viral subpopulations (YMDD variant HBV) with reduced susceptibility to lamivudine have been identified during extended therapy. In controlled trials, when patients developed YMDD mutant HBV, they had a rise in HBV DNA and ALT from previous on-treatment levels. Progression of hepatitis B has been reported in some patients with YMDD mutant HBV. The long term clinical significance if these variants is yet to be fully established.

Co-infection with HIV:

There are no adequate clinical data on the treatment with lamivudine of patients coinfected with HIV and Hepatitis B virus. Zeffix (lamivudine 100mg) once daily is not an appropriate dose or dose frequency for use in the treatment of patients with HIV infection. Co-infected patients requiring lamivudine therapy for HIV should be treated with the dose, dose frequency and appropriate use as set out in the product information for lamivudine 150 mg tablets (3TC™) and lamivudine/zidovudine combination tablets (Combivir™).

Information for patients:

There are no clinical data on the efficacy of lamivudine 100mg daily in patients coinfected with Hepatitis B virus and Delta virus. There is no information available on maternal-foetal transmission of hepatitis B virus in pregnant women receiving treatment with lamivudine 100mg. The standard recommended procedures for hepatitis B virus immunisation in infants should be followed.

Patients should be advised that therapy with lamivudine 100mg has not been proven to reduce the risk of transmission of hepatitis B virus to others and therefore, appropriate precautions should still be taken.

Diabetes (oral solution only):

Diabetic patients should be advised that each dose of oral solution (100mg = 20 mL) contains 4 g of sucrose.

Carcinogenicity, mutagenicity and impairment of fertility:

When lamivudine was administered orally to separate groups of rodents at doses of up to 2000 (mice and male rats) or 3000 (female rats) mg/kg/day, there was no evidence of a carcinogenic effect in the mouse study, nor in male rats (at 37 and 133 times the estimated human exposure, based on AUC, respectively). In female rats, no increase in tumours was observed at the intermediate dose of 1000 mg/kg/day, which resulted in a systemic exposure based on AUC 78 times the estimated human exposure. However, there was an increase in endometrial tumors in females rats at the highest dose (9% tumour incidence) compared with controls (4% incidence). The high dose in female rats resulted in a systemic exposure 220 times the estimated human exposure based on AUC. The relationship of the increase in tumours to treatment is uncertain.
Animal Toxicity
Administration of lamivudine in animal toxicity studies at high doses was not associated with any major organ toxicity. At the highest dosage levels, minor effects on indicators of liver and kidney function were seen together with occasional reduction in liver weights. Reduction of erythrocytes and neutrophil counts were identified as the effects most likely to be of clinical relevance. These events were seen infrequently in clinical studies.

Lamivudine was not mutagenic in Salmonella typhimurium or E. coli reverse mutation assays with and without metabolic activation but did induce mutations at the thymidine kinase locus of the mouse lymphoma L5178Y cells without metabolic activation and was clastogenic in human peripheral blood lymphocytes, with and without metabolic activation in vitro. In rats, an oral dose of lamivudine 2000 mg/kg did not cause chromosomal aberrations in bone marrow cells, nor unscheduled DNA synthesis in primary hepatocytes in vivo. Three consecutive daily oral doses of lamivudine 2000mg/kg in rats, resulting in a systemic exposure (based on C_max) of at least 56 times the clinical exposure, did not induce micronuclei in bone marrow in vivo.

Lamivudine was not genotoxic in vivo at doses that gave plasma concentrations around 60-70 times higher than the anticipated clinical plasma levels. As the in vitro mutagenic activity of lamivudine could not be confirmed by in vivo tests, it is concluded that lamivudine should not represent a genotoxic hazard to patients undergoing treatment.

No evidence of impaired fertility was seen in rats administered lamivudine at oral doses up to 2000 mg/kg BID, resulting in a maximum systemic exposure (based on C_max) of at least 59 times those observed at the clinical dosage.

Use in Pregnancy: Pregnancy category B3

There are limited data available on the safety of lamivudine in human 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.

Lamivudine crosses the placenta in rats and rabbits. No evidence of teratogenicity was observed in rats and rabbits at oral doses up to 2000 and 500 mg/kg BID, respectively, resulting in systemic exposures of at least 51 and 45 times (based on C_max), respectively, of those observed at the clinical dosage. However, embryonic loss was increased, with consequent reduction in litter size, in rabbits at oral doses of 20 mg/kg BID and above, resulting in systemic exposures (based on both C_max and AUC) comparable to those observed at the clinical dosage. No embryonic loss occurred in rats at systemic exposures of at least 51 times the clinical exposure (C_max).

The safety of lamivudine has not been established in human pregnancy. 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, Zeffix administration is not recommended during the first three months of pregnancy.

Lactation:
Following oral administration lamivudine was excreted in human breast milk at similar concentrations to those found in serum (range 1- 8 μg/mL). The safety of lamivudine has not
been established in breast fed infants. No effects were observed in neonatal rats which received lamivudine via maternal milk and supplemented with oral (gavage) dosing, resulting in systemic exposures ($C_{\text{max}}$) of 16 to 19 times those observed at the clinical dosage.

**Interaction with Other Medicines:**

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 e.g. trimethoprim. Other drugs (e.g. ranitidine, cimetidine) are eliminated only in part by this mechanism and were shown not to interact with lamivudine.

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 lamivudine.

Administration of trimethoprim, as trimethoprim/sulfamethoxazole 160 mg/800 mg, causes an increase of about 40% in lamivudine plasma levels. However, unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary. Lamivudine has no effect on the pharmacokinetics of trimethoprim/sulfamethoxazole. Administration of lamivudine in patients with renal impairment should be assessed carefully.

A modest increase in $C_{\text{max}}$ (28%) 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 (see Pharmacokinetics).

Lamivudine 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 Zeffix concurrently with commonly used immunosuppressant drugs (e.g. cyclosporin A). However, formal interaction studies have not been performed.

Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicinal products are used concurrently. Zeffix is therefore not recommended to be used in combination with zalcitabine.

**Effects on the Ability to Drive and Operate Machinery:** 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 the drug. 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.

**ADVERSE REACTIONS:**

**Clinical Trial Information**

**Adults**
In clinical studies of patients with chronic hepatitis B, lamivudine 100mg was well tolerated. The incidence of adverse events and laboratory abnormalities (with the exception of elevations of ALT and CPK, see below) were similar between placebo and lamivudine 100mg treated patients. The most common adverse events reported were malaise and fatigue, respiratory tract infections, headache, abdominal discomfort and pain, nausea, vomiting and diarrhoea. The clinical adverse events occurring at an incidence of 1% or greater in controlled clinical trials and considered to be possibly, probably or almost certainly related to lamivudine are shown in Table 1. A dash represents an incidence of less than 1%.

Table 1 - Clinical adverse events almost certainly, probably or possibly related to lamivudine therapy occurring with an incidence of ≥1% in controlled clinical trials

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Placebo Number of Patients (%)</th>
<th>Lamivudine 100mg daily Number of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 144)</td>
<td>(n = 297)</td>
</tr>
<tr>
<td>Neurology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>14 (10%)</td>
<td>27 (9%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4 (3%)</td>
<td>11 (4%)</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>3 (2%)</td>
<td>10 (3%)</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>5 (3%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Hypoaesthesia</td>
<td>2 (1%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Hypnagogic effects</td>
<td>0</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea &amp; vomiting</td>
<td>11 (8%)</td>
<td>21 (7%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>8 (6%)</td>
<td>15 (5%)</td>
</tr>
<tr>
<td>Abdominal discomfort &amp; pain</td>
<td>5 (3%)</td>
<td>12 (4%)</td>
</tr>
<tr>
<td>Gaseous symptoms</td>
<td>3 (2%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Non-site specific</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malaise &amp; fatigue</td>
<td>19 (13%)</td>
<td>39 (13%)</td>
</tr>
<tr>
<td>Hepatobiliary Tract &amp; Pancreas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal liver function tests</td>
<td>1 (---)</td>
<td>21 (7%)</td>
</tr>
<tr>
<td>Abnormal pancreatic enzymes</td>
<td>4 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin rashes</td>
<td>6 (4%)</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Hair loss &amp; alopecia</td>
<td>1 (---)</td>
<td>7 (2%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2 (1%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Acne &amp; folliculitis</td>
<td>0</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Endocrine &amp; Metabolic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal enzyme levels</td>
<td>3 (2%)</td>
<td>8 (3%)</td>
</tr>
<tr>
<td>Eating problems</td>
<td>3 (2%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Disorders of thirst/fluid intake</td>
<td>1 (---)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle pain</td>
<td>2 (1%)</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>Psychiatry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive orders</td>
<td>1 (---)</td>
<td>4 (1%)</td>
</tr>
</tbody>
</table>
Blood & Lymphatic

| Decreased white cells | 0 | 3 (1%) |

Lower Respiratory

| Viral respiratory infection | 0 | 3 (1%) |

**Clinical trial data:**

**Elevations of ALT**

Elevations in ALT were more common post-treatment in patients treated with Zefix 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 Zefix and placebo treated patients. The relationship of these recurrent hepatitis events to Zefix treatment or to the previous underlying disease is uncertain (see Special Warnings and Special Precautions for Use).

**Elevations of CPK**

**Observed During Clinical Practice:** In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of Zefix.

- Thrombocytopenia.
- Muscle disorders, including myalgia, cramps and rhabdomyolysis.

**Children and Adolescents:**

In clinical studies of paediatric and adolescent patients with chronic hepatitis B, lamivudine 100mg was well tolerated. The incidence of adverse events was similar between placebo and lamivudine 100mg treated patients and is consistent with those seen in the adult patient population. The most common adverse events reported were abdominal discomfort and pain and headache. The clinical adverse events occurring at an incidence of 3% or greater in controlled clinical trials and considered to be possibly, probably or almost certainly related to lamivudine are shown in Table 2.

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**Table 2** - Clinical adverse events almost certainly, probably or possibly related to lamivudine therapy occurring with an incidence of ≥3% in study NUC30903
<table>
<thead>
<tr>
<th>Drug-Related Event</th>
<th>Placebo N=96</th>
<th>Lamivudine N=191</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Discomfort &amp; Pain</td>
<td>8 (8)</td>
<td>8 (4)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (5)</td>
<td>11 (6)</td>
</tr>
<tr>
<td>Abnormal Liver Function Tests</td>
<td>4 (4)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Malaise &amp; Fatigue</td>
<td>3 (3)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Nausea &amp; vomiting</td>
<td>3 (3)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Skin rashes</td>
<td>2 (2)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>4 (4)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Feeding Problems</td>
<td>4 (4)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>2 (2)</td>
<td>5 (3)</td>
</tr>
</tbody>
</table>

Post-marketing information:

There is no post-marketing experience with the use of lamivudine 100mg daily for the treatment of hepatitis B virus.

DOSAGE AND ADMINISTRATION:

Adults and adolescents 12 years and older: the recommended dosage of Zeffix is 100 mg once daily.

Children from two to eleven years*: the recommended dose is 3 mg/kg once daily up to a maximum of 100 mg daily.

*The effectiveness of treatment beyond 1 year in children aged from 2 – 17 years and the optimum duration of treatment for this group has not been established. (see Clinical Trials).

Children less than two years: there are insufficient data available to propose specific dosage recommendations in this age group.

Zeffix oral solution is available for use in children and for those patients for whom the tablets are inappropriate.

Food reduces the $C_{\text{max}}$ and extends the $T_{\text{max}}$, but the amount of drug absorbed is not reduced. These changes to the pharmacokinetic parameters are not statistically or clinically significant (see Pharmacokinetics).

Discontinuation of Zeffix 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. There are limited data regarding the maintenance of seroconversion long term after stopping treatment with Zeffix.

Patient compliance should be monitored while on Zeffix therapy. If Zeffix is discontinued, patients should be periodically monitored for evidence of recurrent hepatitis (see PRECAUTIONS).

Renal impairment

Lamivudine serum concentrations 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 < 50 mL/minute (see Table 3 for adults & Table 4 for children 2 – 11 years of age). When doses less than 100mg are required Zeffix oral solution should be used. The same percentage reduction in dose applies for children with renal impairment (see Table 4 below).

Table 3 Dosing recommendations – adults and adolescents 12 years and older.

<table>
<thead>
<tr>
<th>Creatinine clearance mL/min</th>
<th>First Dose of Zeffix oral solution *</th>
<th>Maintenance Dose Once Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 to &lt;50</td>
<td>20 mL (100mg)</td>
<td>10 mL (50 mg)</td>
</tr>
<tr>
<td>15 to &lt; 30</td>
<td>20 mL (100mg)</td>
<td>5 mL (25 mg)</td>
</tr>
<tr>
<td>5 to &lt;15</td>
<td>7 mL (35 mg)</td>
<td>3 mL (15 mg)</td>
</tr>
<tr>
<td>&lt;5</td>
<td>7 mL (35 mg)</td>
<td>2 mL (10 mg)</td>
</tr>
</tbody>
</table>

* Zeffix oral solution containing 5mg/mL lamivudine.

Table 4 Dosing recommendations – children 2 to 11 years.

<table>
<thead>
<tr>
<th>Creatinine clearance mL/min</th>
<th>First Dose of Zeffix oral solution *</th>
<th>Maintenance Dose Once Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 to &lt;50</td>
<td>3 mg/kg</td>
<td>1.5 mg/kg</td>
</tr>
<tr>
<td>15 to &lt;30</td>
<td>3 mg/kg</td>
<td>0.75 mg/kg</td>
</tr>
<tr>
<td>5 to &lt;15</td>
<td>1 mg/kg</td>
<td>0.45 mg/kg</td>
</tr>
<tr>
<td>&lt;5</td>
<td>1 mg/kg</td>
<td>0.3 mg/kg</td>
</tr>
</tbody>
</table>

* Zeffix oral solution containing 5mg/ml lamivudine.

Data available in patients undergoing intermittent haemodialysis (4hrs dialysis 2-3 times weekly), indicate that following the initial dosage reduction of Zeffix 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.

**OVERDOSAGE:**

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.
PRESENTATION:

Tablets:
Zeffix tablets are supplied in blister packs containing 28 tablets or 84 tablets*. Each tablet contains 100mg of lamivudine.

The tablets are butterscotch coloured, film coated, capsule shaped, biconvex and engraved “GX CG5” on one face.

Zeffix tablets also contain microcrystalline cellulose (460), sodium starch glycollate, magnesium stearate (572), hypromellose (464), titanium dioxide (171), macrogol, polysorbate 80 (433), yellow iron oxide Cl 77192 and red iron oxide Cl 77491.

Oral Solution:
Zeffix oral solution is supplied in an opaque white HDPE bottle, with a child-resistant cap. The bottle contains 240 mL of Zeffix solution, for oral use only, and is in a carton. The pack includes a clear polypropylene oral dosing syringe and polyethylene syringe-adapter.

Zeffix oral solution contains 5 mg/mL lamivudine and 20% (w/v) sucrose.

Zeffix oral solution also contains methyl hydroxybenzoate (218), propyl hydroxybenzoate (216), citric acid anyhydrous, propylene glycol, sodium citrate, artificial strawberry flavouring, artificial banana flavouring and purified water.

NAME AND ADDRESS OF SPONSOR:

GlaxoSmithKline Australia Pty Ltd
1061 Mountain Highway
Boronia Victoria 3155

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Date of Last Safety Related Notification: 1 August 2006
Issue No. 7

*: Pack size not currently marketed.