Zeffix Tablets
Lamivudine

QUALITATIVE AND QUANTITATIVE COMPOSITION

The tablets are butterscotch coloured, film-coated, capsule shaped, biconvex and engraved "GX CG5" on one face. Each tablet contains lamivudine 100mg.

PHARMACEUTICAL FORM

Film-coated tablets

CLINICAL PARTICULARS

Indications

Zeffix is indicated for the treatment of patients ≥ 16 years of age with chronic hepatitis B and evidence of hepatitis B virus (HBV) replication with one or more of the following conditions:
- elevated serum alanine aminotransferase (ALT) ≥ 2 times normal
- liver cirrhosis
- decompensated liver disease
- biopsy-proven necro-inflammatory liver disease
- immunocompromised state
- liver transplant

Dosage and Administration

The recommended dosage of Zeffix is 100mg once daily.

Zeffix can be taken with or without food.

Optimum duration of therapy has not been established.

Discontinuation of Zeffix may be considered in the following situation:
- in immunocompetent patients with HBeAg and/or HBsAg seroconversion confirmed
- when a female patient becomes pregnant during therapy
- when a patient shows signs of intolerance to Zeffix while on treatment
- where in the treating doctor's opinion, there is a loss of efficacy of Zeffix e.g. when persistent return of serum ALT to pre-treatment values or when the patient experiences deterioration in liver histology

Patient compliance should be monitored while on Zeffix therapy. If Zeffix 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 Zeffix.

Zeffix should be used in accordance with available official recommendations.

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 < 50 ml/minute.

When doses below 100 mg are required Zeffix oral solution should be used (see table below, Table 1).

Table 1.

Creatinine clearance ml/min	**First Dose of Zeffix Oral solution ***	**Maintenance Dose Once Daily**
30 to <50	20 ml (100 mg)	10 ml (50 mg)
15 to <30	20 ml (100 mg)	5 ml (25 mg)
5 to <15	7 ml (35 mg)	3 ml (15 mg)
<5	7 ml (35 mg)	2 ml (10 mg)

* 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.

Contraindications

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

Warnings and Precautions

Initiation of lamivudine 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 with Zeffix patients should be monitored regularly by a physician experienced in the management of chronic hepatitis B. Serum ALT levels should be monitored at 3 months intervals and HBV DNA and HBeAg should be assessed every 6 months.

If Zeffix is discontinued or there is a loss of efficacy due to the development of YMDD variant HBV, some patients may experience clinical or laboratory evidence of recurrent hepatitis. If Zeffix 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 Zeffix treatment. Exacerbation of hepatitis has primarily been detected by serum ALT elevations, in addition to the re-emergence of HBV DNA. See Table 4 in *Pharmacological Properties, Clinical Studies* for more information regarding frequency of post treatment ALT elevations. Most events appear to have been self-limited. Fatalities are very rare and the causal relationship to discontinuation of lamivudine treatment is unknown.

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 section *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 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 at least every month. If treatment is discontinued for any reason, it is recommended that these patients are monitored for at least 6 months post cessation of treatment. Laboratory parameters to be monitored should include (as a minimum) serum ALT, bilirubin, albumin, blood urea nitrogen, creatinine, and virological status: HBV antigen/antibody, and serum HBV DNA concentrations when possible. Patients experiencing signs of hepatic insufficiency during or post-treatment should be monitored frequently, as appropriate.

There are limited data on the use of lamivudine 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 (*see Clinical Studies).*

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.

For HIV co-infected patients not requiring anti-retroviral therapy, there is a risk of HIV mutation when using lamivudine alone for treating chronic hepatitis B.

There is limited information available on maternal-foetal transmission of hepatitis B virus in pregnant women receiving treatment with Zeffix. The standard recommended procedures for hepatitis B virus immunisation in infants should be followed.

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

Interactions

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.

Interactions relevant to lamivudine

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

Zidovudine: A modest increase in C_{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*).

Emtricitabine: Lamivudine may inhibit the intracellular phosphorylation of emtricitabine when the two medicinal products are used concurrently. Lamivudine 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 C_{max} of lamivudine in adults. When possible, avoid use of lamivudine with sorbitol-containing medicines or consider more frequent monitoring of HBV viral load when chronic coadministration cannot be avoided.

Alpha-interferon: 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.

Pregnancy and Lactation

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 (see *Clinical Studies*). 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 lamivudine crosses the placenta.

Use in pregnancy should be considered only if the benefit outweighs the risk. Although the results of animal studies (*see Pre-clinical safety data)* are not always predictive of human response, there was no evidence of teratogenicity in animals but, findings in the rabbit suggest a potential risk of early embryonic loss that was not observed in the rat.

For patients who are being treated with Zeffix and subsequently become pregnant consideration should be given to the possibility of a recurrence of hepatitis on discontinuation of Zeffix (see *Warnings and Precautions*).

Lactation

Following oral administration, lamivudine was excreted in breast milk at similar concentrations to those found in serum. It is therefore recommended that mothers taking lamivudine do not breast feed their infants.

Effects on Ability to 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 would not be predicted from the pharmacology of the drug.

Adverse Reactions

Clinical Trial Data

In clinical studies of patients with chronic hepatitis B, Zeffix 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 Zeffix treated patients (see Table 2). The most common adverse events reported were malaise and fatigue, respiratory tract infections, headache, abdominal discomfort and pain, nausea, vomiting and diarrhoea.

Table 2.

Adverse event	Clinical trial data: Integrated phase III data	
	Placebo (n=200)	Lamivudine 100mg (n=416)
Malaise & Fatigue	28%	26%
Respiratory tract infection	17%	19%
Headache	21%	22%
Abdominal discomfort & pain	17%	15%
Nausea & vomiting	17%	16%
Diarrhoea	12%	14%
ALT elevations during treatment[1]	13%	13%
ALT elevations post treatment[2]	8%	19%
Elevated CPK[1]	5%	9%

[1] Percentage of patients experiencing a grade III or IV laboratory abnormality during treatment.

[2] Percentage of patients experiencing a grade III or IV elevation in ALT post-treatment.

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 Zeffix. 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).

The frequency categories assigned to the adverse reactions below are estimates: for most events, suitable data for calculating incidence are not available. Very common and common adverse drug reaction frequency categories were determined from clinical trial data and the background incidence in placebo groups was not taken into

account. Adverse drug reactions identified through post-marketing surveillance were categorised as rare or very rare.

Hepato-biliary disorders
Very common: Elevations of ALT

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

Skin and subcutaneous tissue disorder
Common: Rash

Musculoskeletal, connective tissue and bone 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 Zeffix.

Blood and the lymphatic system disorders
Very Rare: Thrombocytopenia.

Musculoskeletal, connective tissue and bone disorders
Common: Muscle disorders, including myalgia and cramps.

Very rare: Rhabdomyolysis.

In patients with HIV infection, cases of pancreatitis and peripheral neuropathy (or parasthesia) 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 Zeffix 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.

Overdose

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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Lamivudine 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 17-19 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.

Clinical Studies

Experience in patients with HBeAg positive CHB and compensated liver disease: in controlled studies, 1 year of lamivudine therapy significantly suppressed HBV DNA replication [34-57 % of patients were below the assay detection limits (Abbott Genostics solution hybridization assay, LLOD < 1.6pg/ml)], normalised ALT level (40-72 % of patients), induced HBeAg seroconversion (HBeAg loss and HBeAb detection with HBV DNA loss [by conventional assay], 16-18 % of patients), improved histology (38-52 % of patients had a $\geq$2 point decrease in the Knodell Histologic Activity Index [HAI]) and reduced progression of fibrosis (in 3-17 % of patients) and progression to cirrhosis.

Continued lamivudine treatment for an additional 2 years in patients who had failed to achieve HBeAg seroconversion in the initial 1 year controlled studies resulted in further improvement in bridging fibrosis. In patients with YMDD variant HBV, 41/82 (50 %) patients had improvement in liver inflammation and 40/56 (71 %) patients without YMDD variant HBV had improvement. Improvement in bridging fibrosis occurred in 19/30 (63 %) patients without YMDD variant and 22/44 (50 %) patients with the variant. Five percent (3/56) of patients without the YMDD variant and 13 % (11/82) of patients with YMDD variant showed worsening in liver inflammation compared to pre-treatment. Progression to cirrhosis occurred in 4/68 (6 %) patients

with the YMDD variant, whereas no patients without the variant progressed to cirrhosis.

In an extended treatment study in Asian patients (NUCB3018) the HBeAg seroconversion rate and ALT normalisation rate at the end of the 5 year treatment period was 48 % (28/58) and 47 % (15/32), respectively. HBeAg seroconversion was increased in patients with elevated ALT levels; 77 % (20/26) of patients with pre-treatment ALT> 2 x ULN seroconverted. At the end of 5 years, all patients had HBV DNA levels that were undetectable or lower than pre-treatment levels.
Further results from the trial by YMDD variant status are summarised in Table 3.

Table 3: Efficacy results 5 years by YMDD status (Asian Study) NUCB3018

	Subjects, % (no.)			
YMDD variant HBV status	YMDD[1]		Non-YMDD[1]	
HBeAg seroconversion				
All patients	38	(15/40)	72	(13/18)
- Baseline ALT ≤1 x ULN[2]	9	(1/11)	33	(2/6)
- Baseline ALT > 2 x ULN	60	(9/15)	100	(11/11)
Undetectable HBV DNA				
- Baseline[3]	5	(2/40)	6	(1/18)
- Week 260[4]				
Negative	8	(2/25)	0	
positive < baseline	92	(23/25)	100	(4/4)
positive > baseline	0		0	
ALT normalisation				
- Baseline				
Normal	28	(11/40)	33	(6/18)
above normal	73	(29/40)	67	(12/18)
- Week 260				
Normal	46	(13/28)	50	(2/4)
above normal < baseline	21	(6/28)	0	
above normal > baseline	32	(9/28)	50	(2/4)

[1] Patients designated as YMDD variant were those with ≥5% YMDD variant HBV at any annual time-point during the 5-year period. Patients categorised as non-YMDD variant were those with > 95% wild-type HBV at all annual time-points during the 5-year study period
[2] Upper limit of normal

[3] Abbott Genostics solution hybridisation assay (LLOD < 1.6 pg/ml)
[4] Chiron Quantiplex assay (LLOD 0.7 Meq/ml)

Comparative data according to YMDD status were also available for histological assessment but only up to three years. In patients with YMDD variant HBV, 18/39 (46 %) had improvements in necroinflammatory activity and 9/39 (23 %) had worsening. In patients without the variant, 20/27 (74 %) had improvements in necroinflammatory activity and 2/27 (7 %) had worsening.

Following HBeAg seroconversion, serologic response and clinical remission are generally durable after stopping lamivudine. However, relapses have been identified in patients although they obtained HBeAg seroconversion. Therefore, following HBeAg seroconversion, patients should be periodically monitored to determine that serologic and clinical responses are being maintained. In patients who do not maintain a sustained serological response, consideration should be given to retreatment with either lamivudine or an alternative antiviral agent for resumption of clinical control of HBV.

In patients followed for up to 16 weeks after discontinuation of treatment at one year, post-treatment ALT elevations were observed more frequently in patients who had received lamivudine than in patients who had received placebo. A comparison of post-treatment ALT elevations between weeks 52 and 68 in patients who discontinued lamivudine at week 52 and patients in the same studies who received placebo throughout the treatment course is shown in Table 4. The proportion of patients who had post-treatment ALT elevations in association with an increase in bilirubin levels was low and similar in patients receiving either lamivudine or placebo.

Table 4: Post-treatment ALT Elevations in 2 Placebo‑Controlled Studies in Adults

	Patients with ALT Elevation/ Patients with Observations*	
Abnormal Value	Lamivudine	Placebo
ALT ≥2 x baseline value	37/137 (27 %)	22/116 (19 %)
ALT ≥3 x baseline value[†]	29/137 (21 %)	9/116 (8 %)
ALT ≥2 x baseline value and absolute ALT > 500 IU/l	21/137 (15 %)	8/116 (7 %)
ALT ≥2 x baseline value; and bilirubin > 2 x ULN and ≥2 x baseline value	1/137 (0.7 %)	1/116 (0.9 %)

*Each patient may be represented in one or more category.
[†]Comparable to a Grade 3 toxicity in accordance with modified WHO criteria.
ULN = Upper limit of normal.

Experience in patients with HBeAg negative CHB: initial data indicate the efficacy of lamivudine in patients with HBeAg negative CHB is similar to patients with HBeAg positive CHB, with 71 % of patients having HBV DNA suppressed below the

detection limit of the assay, 67 % ALT normalisation and 38 % with improvement in HAI after one year of treatment. When lamivudine was discontinued, the majority of patients (70 %) had a return of viral replication. Data is available from an extended treatment study in HBeAg negative patients (NUCAB3017) treated with lamivudine. After two years of treatment in this study, ALT normalisation and undetectable HBV DNA occurred in 30/69 (43 %) and 32/68 (47 %) patients respectively and improvement in necroinflammatory score in 18/49 (37 %) patients. In patients without YMDD variant HBV, 14/22 (64 %) showed improvement in necroinflammatory score and 1/22 (5 %) patients worsened compared to pre-treatment. In patients with the variant, 4/26 (15 %) patients showed improvement in necroinflammatory score and 8/26 (31 %) patients worsened compared to pre-treatment. No patients in either group progressed to cirrhosis.

Frequency of emergence of YMDD variant HBV and impact on the treatment response: lamivudine monotherapy results in the selection of YMDD variant HBV in approximately 24 % of patients following one year of therapy, increasing to 69% following 5 years of therapy. Development of YMDD variant HBV is associated with reduced treatment response in some patients, as evidenced by increased HBV DNA levels and ALT elevations from previous on-therapy levels, progression of signs and symptoms of hepatitis disease and/or worsening of hepatic necroinflammatory findings. Given the risk of YMDD mutant HBV, maintenance of lamivudine monotherapy is not appropriate in patients with detectable serum HBV DNA at or beyond 24 weeks of treatment (see *Warnings and Precautions*).

In a double-blind study in CHB patients with YMDD variant HBV and compensated liver disease (NUC20904), with a reduced virological and biochemical response to lamivudine (n=95), the addition of adefovir dipivoxil 10 mg once daily to ongoing lamivudine 100mg for 52 weeks resulted in a median decrease in HBV DNA of 4.6 $\log_{10}$ copies/ml compared to a median increase of 0.3 $\log_{10}$ copies/ml in those patients receiving lamivudine monotherapy. Normalisation of ALT levels occurred in 31 % (14/45) of patients receiving combined therapy versus 6 % (3/47) receiving lamivudine alone.

Forty patients (HBeAg negative or HBeAg positive) with either decompensated liver disease or recurrent HBV following liver transplantation and YMDD variant were also enrolled into an open label arm of the study. Addition of 10 mg adefovir dipivoxil once daily to ongoing lamivudine 100mg for 52 weeks resulted in a median decrease in HBV DNA of 4.6 $\log_{10}$ copies/ml. Improvement in liver function was also seen after one year of therapy.

Experience in patients with decompensated liver disease: placebo controlled studies have been regarded as inappropriate in patients with decompensated liver disease, and have not been undertaken. In non-controlled studies, where lamivudine was administered prior to and during transplantation, effective HBV DNA suppression and ALT normalisation was demonstrated. When lamivudine therapy was continued post transplantation there was reduced graft re-infection by HBV, increased HBsAg loss and on one-year survival rate of 76 – 100 %.

As anticipated due to the concomitant immunosuppression, the rate of emergence of YMDD variant HBV after 52 weeks treatment was higher (36 % - 64 %) in the liver transplant population than in the immunocompetent CHB patients (14 % - 32 %).

Experience in CHB patients with advanced fibrosis or cirrhosis: in a placebo-controlled study in 651 patients with clinically compensated chronic hepatitis B and histologically confirmed fibrosis or cirrhosis, lamivudine treatment (median duration 32 months) significantly reduced the rate of overall disease progression (34/436, 7.8 % for lamivudine versus 38/215, 17.7 % for placebo, p=0.001), demonstrated by a significant reduction in the proportion of patients having increased Child-Pugh scores (15/436, 3.4 % versus 19/215, 8.8 %, p=0.023) or developing hepatocellular carcinoma (17/436, 3.9 % versus 16/215, 7.4 %, p=0.047). The rate of overall disease progression in the lamivudine group was higher for subjects with detectable YMDD variant HBV DNA (23/209, 11 %) compared to those without detectable YMDD variant HBV (11/221, 5 %). However, disease progression in YMDD subjects in the lamivudine group was lower than the disease progression in the placebo group (23/209, 11 % versus 38/214, 18 % respectively). Confirmed HBeAg seroconversion occurred in 47 % (118/252) of subjects treated with lamivudine and 93 % (320/345) of subjects receiving lamivudine became HBV DNA negative (VERSANT [version 1], bDNA assay, LLOD < 0.7 MEq/ml) during the study.

Experience in children and adolescents: lamivudine has been administered to children and adolescents with compensated CHB in a placebo controlled study of 286 patients aged 2 to 17 years. This population primarily consisted of children with minimal hepatitis B. A dose of 3 mg/kg once daily (up to a maximum of 100 mg daily) was used in children aged 2 to 11 years and a dose of 100 mg once daily in adolescents aged 12 years and above. This dose needs to be further substantiated. The difference in the HBeAg seroconversion rates (HBeAg and HBV DNA loss with HBeAb detection) between placebo and lamivudine was not statistically significant in this population (rates after one year were 13 % (12/95) for placebo versus 22 % (42/191) for lamivudine; p=0.057). The incidence of YMDD variant HBV was similar to that observed in adults, ranging from 19 % at week 52 up to 45 % in patients treated continuously for 24 months.

The Antiretroviral Pregnancy Registry has received reports of over 11,000 exposures to lamivudine during pregnancy resulting in live birth, less than 1 % of which were in patients with HBV. These consist of over 4,500 exposures during the first trimester, over 7,200 exposures during the second/third trimester and included 143 and 207 major birth defects respectively. The prevalence (95 % CI) of defects in the first trimester was 3.1 % (2.6, 3.7 %) and in the second/third trimester, 2.9 % (2.5, 3.3 %). Among pregnant women in the reference population, the background rate of birth defects is 2.7 %.

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 therapeutic dose levels i.e. 100 mg once daily, C_{max} is in the order of 1.1-1.5 μg/ml and trough levels were 0.015- 0.020 μg/ml.

Co-administration of lamivudine with food resulted in a delay of t_{max} and a lower C_{max} (decreased by up to 47 %). However, the extent (based on the AUC) of lamivudine absorbed was not influenced, therefore Zeffix can be administered with or without food.

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 shows lamivudine penetrates the central nervous system and reaches the cerebro-spinal 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 *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 P-glycoprotein (Pgp), multidrug and toxin extrusion protein 1 (MATE1), MATE2K 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 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:

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

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 parameters 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 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 <50 ml/min (see *Dosage and Administration*).

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.

Pre-clinical Safety Data

Reproductive studies in animals have not shown evidence of teratogenicity and showed no effect on male or female fertility in rats. Lamivudine produced small increases in early embryonic loss when administered to pregnant rabbits, at exposure levels comparable to those achieved in man. However, there was no evidence of embryonic loss in rats at exposure levels of approximately 60 times the clinical exposure (based on C_{max}).

PHARMACEUTICAL PARTICULARS

Special Precautions for Storage

Store below 30ºC.

Zeffix is a trademark of the GSK Group of Companies.

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(GSK Logo)