Zeffix® 100 mg

Film-coated tablets
Lamivudine

NAME OF THE MEDICINAL PRODUCT
Zeffix 100 mg film-coated tablets
QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 100 mg lamivudine
For the full list of excipients see "List of excipients".
PHARMACEUTICAL FORM
Film-coated tablet (tablet)
Butterscotch coloured, film-coated, capsule shaped, biconvex tablets engraved "GX CG5" on one face.
CLINICAL PARTICULARS
Therapeutic indications
Zeffix is indicated for the treatment of chronic hepatitis B in adults with:

- compensated liver disease with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active liver inflammation and/or fibrosis. Initiation of lamivudine treatment should only be considered when the use of an alternative antiviral agent with a higher genetic barrier is not available or appropriate (see "Pharmacodynamic properties").
- decompensated liver disease in combination with a second agent without cross-resistance to lamivudine (see "Posology and method of administration").

Posology and method of administration
Therapy with Zeffix should be initiated by a physician experienced in the management of chronic hepatitis B.
Posology
Adults
The recommended dosage of Zeffix is 100 mg once daily.
In patients with decompensated liver disease, lamivudine should always be used in combination with a second agent, without cross-resistance to lamivudine, to reduce the risk of resistance and to achieve rapid viral suppression.
Duration of treatment
The optimal duration of treatment is unknown.

- In patients with HBeAg positive chronic hepatitis B (CHB) without cirrhosis, treatment should be administered for at least 6-12 months after HBeAg seroconversion (HBeAg and HBV DNA loss with HBeAb detection) is confirmed, to limit the risk of virological relapse, or until HBsAg seroconversion or there is loss of efficacy (see "Special warnings and precautions for use"). Serum ALT and HBV DNA levels should be followed regularly after treatment discontinuation to detect any late virological relapse.
- In patients with HBeAg negative CHB (pre-core mutant) without cirrhosis, treatment should be administered at least until HBs seroconversion or there is evidence of loss of efficacy. With prolonged treatment, regular reassessment is recommended to confirm that continuation of the selected therapy remains appropriate for the patient.
- In patients with decompensated liver disease or cirrhosis and in liver transplant recipients, treatment cessation is not recommended (see "Pharmacodynamic properties").

If lamivudine is discontinued, patients should be periodically monitored for evidence of recurrent hepatitis (see "Special warnings and precautions for use").
Clinical resistance
In patients with either HBeAg positive or HBeAg negative CHB, the development of YMDD (tyrosine-methionine-aspartate-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 based on therapeutic guidelines should be considered if serum HBV DNA remains detectable at or beyond 24 weeks of treatment
(see "Pharmacodynamic properties").
For the treatment of patients who are co-infected with HIV and are currently receiving or plan to receive treatment with lamivudine or the combination lamivudine-zidovudine, the dose of lamivudine prescribed for HIV infection (usually 150 mg/twice daily in combination with other antiretrovirals) should be maintained.
Special populations:

- **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 1 below).
Table 1: Dosage of Zeffix in patients with decreased renal clearance.

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 5 mg/ml lamivudine.
Data available in patients undergoing intermittent haemodialysis (for less than or equal to 4 hrs dialysis 2-3 times weekly), indicate that following the initial dosage reduction of lamivudine to correct for the patient's creatinine clearance, no further dosage adjustments are required while undergoing dialysis.

- **Hepatic impairment**

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

- **Elderly**

In elderly patients, normal ageing with accompanying renal decline has no clinically significant effect on lamivudine exposure, except in patients with creatinine clearance of < 50 ml/min.

- **Paediatric population**

The safety and efficacy of Zeffix in infants, children and adolescents aged below 18 years have not been established. Currently available data are described in "Special warnings and precautions for use" and "Pharmacodynamic properties" but no recommendation on a posology can be made.

Method of administration
Oral use.
Zeffix can be taken with or without food.
Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in "List of excipients".
Special warnings and precautions for use
Lactic acidosis and severe hepatomegaly with steatosis
Occurrences of lactic acidosis (in the absence of hypoxaemia), sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of nucleoside analogues. As lamivudine is a nucleoside analogue, this risk cannot be excluded. Treatment with nucleoside analogues should be discontinued when rapidly elevating aminotransferase levels, progressive hepatomegaly or metabolic/lactic acidosis of unknown aetiology occur. Benign digestive symptoms, such as nausea, vomiting and abdominal pain, might be indicative of lactic acidosis development. Severe cases, sometimes with fatal outcome, were associated with pancreatitis, liver failure/hepatic steatosis, renal failure and higher levels of serum lactate. Caution should be exercised when prescribing nucleoside analogues to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicinal products and alcohol). Patients co-infected with hepatitis C and treated with alpha interferon and ribivirin may constitute a special risk. These patients should be followed closely.
Exacerbations of hepatitis
Exacerbations on treatment
Spontaneous exacerbations in chronic hepatitis B are relatively common and are characterised by transient increases in serum ALT. After initiating antiviral therapy, serum ALT may increase in some patients as serum HBV DNA levels decline. In patients with compensated liver disease, these increases in serum ALT were generally not accompanied by an increase in serum bilirubin concentrations or signs of hepatic decompensation.
HBV viral subpopulations with reduced susceptibility to lamivudine (YMDD mutant HBV) have been identified with extended therapy. In some patients the development of YMDD mutant HBV can lead to exacerbation of hepatitis, primarily detected by serum ALT elevations and re-emergence of HBV DNA (see "Posology and method of administration"). In patients who have YMDD mutant HBV, a switch to or addition of an alternative agent without cross resistance to lamivudine based on therapeutic guidelines should be considered (see "Pharmacodynamic properties").
Exacerbations after treatment discontinuation
Acute exacerbation of hepatitis has been observed in patients who have discontinued hepatitis B therapy and is usually detected by serum ALT elevations and re-emergence of HBV DNA. In the controlled Phase III trials with no-active-treatment follow-up, the incidence of post-treatment ALT elevations (more than 3 times baseline) was higher in lamivudine-treated patients (21 %) compared with those receiving placebo (8 %). However, the proportion of patients who had post-treatment elevations associated with bilirubin elevations was low and similar in both treatment arms (see Table 3 in "Pharmacodynamic properties"). For lamivudine-treated patients, the majority of post-treatment ALT elevations occurred between 8 and 12 weeks post-treatment. Most events have been self-limiting, however some fatalities have been observed. 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, and then as clinically indicated.
Exacerbations in patients with decompensated cirrhosis
Transplantation recipients and patients with decompensated cirrhosis are at greater risk from active viral replication. Due to the 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. These patients should be monitored for clinical, virological and serological parameters associated with hepatitis B, liver and renal function, and antiviral response during treatment (at least every month), and, if treatment is discontinued for any reason, for at least 6 months after 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 more frequently as appropriate.
For patients who develop evidence of recurrent hepatitis post-treatment, there are insufficient data on the benefits of re-initiation of lamivudine treatment.
Mitochondrial dysfunction
Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in infants exposed in utero and/or post-natally to nucleoside analogues. The main adverse events reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactatemia, hyperlipasemia). Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). The neurological disorders might be transient or permanent. Any child exposed *in utero* to nucleoside and nucleotide analogues, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in cases which have relevant signs or symptoms.
Paediatric patients
Lamivudine has been administered to children (2 years and above) and adolescents with compensated chronic hepatitis B. However, due to limitations of the data, the administration of lamivudine to this patient population is not currently recommended
(see "Pharmacodynamic properties").
Delta hepatitis or hepatitis C
The efficacy of lamivudine in patients co-infected with Delta hepatitis or hepatitis C has not been established and caution is advised.
Immunosuppressive treatments
Data are limited on the use of lamivudine in HBeAg negative (pre-core mutant) patients and in those receiving concurrent immunosuppressive regimes, including cancer chemotherapy. Lamivudine should be used with caution in these patients.
Monitoring
During treatment with Zeffix patients should be monitored regularly. Serum ALT and HBV DNA levels should be monitored at 3 month intervals and in HBeAg positive patients HBeAg should be assessed every 6 months.
HIV co-infection
For the treatment of patients who are co-infected with HIV and are currently receiving or plan to receive treatment with lamivudine or the combination lamivudine-zidovudine, the dose of lamivudine prescribed for HIV infection (usually 150 mg/twice daily in combination with other antiretrovirals) 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.
Transmission of hepatitis B
There is no information available on maternal-foetal transmission of hepatitis B virus in pregnant women receiving treatment with lamivudine. The standard recommended procedures for hepatitis B virus immunisation in infants should be followed.
Patients should be advised that therapy with lamivudine 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 with other medicinal products
Zeffix should not be taken with any other medicinal products containing lamivudine or medicinal products containing emtricitabine (see "Interaction with other medicinal products and other forms of interaction").
The combination of lamivudine with cladribine is not recommended (see "Interaction with other medicinal products and other forms of interaction").
Interaction with other medicinal products and other forms of interaction
Interaction studies have only been performed in adults.
The likelihood of metabolic interactions is low due to limited metabolism and plasma protein binding and almost complete renal elimination of unchanged substance.
Lamivudine is predominantly eliminated by active organic cationic secretion. The possibility of interactions with other medicinal products administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system e.g. trimethoprim. Other medicinal products (e.g. ranitidine, cimetidine) are eliminated only in part by this mechanism and were shown not to interact with lamivudine.
Substances shown to be predominately excreted either via the active organic anionic pathway, or by glomerular filtration are unlikely to yield clinically significant interactions with lamivudine.
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.
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 "Pharmacokinetic properties").
Lamivudine has no pharmacokinetic interaction with alpha-interferon when the two medicinal products are concurrently administered. There were no observed clinically significant adverse interactions in patients taking lamivudine concurrently with commonly used immunosuppressant medicinal products (e.g. cyclosporin A). However, formal interaction studies have not been performed.
Emtricitabine
Due to similarities, Zeffix should not be administered concomitantly with other cytidine analogues, such as emtricitabine. Moreover, Zeffix should not be taken with any other medicinal products containing lamivudine (see "Special warnings and precautions for use").
Cladribine
In vitro lamivudine inhibits the intracellular phosphorylation of cladribine leading to a potential risk of cladribine loss of efficacy in case of combination in the clinical setting. Some clinical findings also support a possible interaction between lamivudine and cladribine. Therefore, the concomitant use of lamivudine with cladribine is not recommended (see "Special warnings and precautions for use").
Fertility, pregnancy and lactation
Pregnancy
A large amount of data on pregnant women (more than 1000 exposed outcomes) indicate no malformative toxicity. Zeffix can be used during pregnancy if clinically needed.
For patients who are being treated with lamivudine and subsequently become pregnant consideration should be given to the possibility of a recurrence of hepatitis on discontinuation of lamivudine.
Breast-feeding
Based on more than 200 mother/child pairs treated for HIV, serum concentrations of lamivudine in breastfed infants of mothers treated for HIV are very low (less than 4 % of maternal serum concentrations) and progressively decrease to undetectable levels when breastfed infants reach 24 weeks of age. The total amount of lamivudine ingested by a breastfed infant is very low and is therefore likely to result in exposures exerting a sub-optimal antiviral effect. Maternal hepatitis B is not a contraindication to breast-feeding if the newborn is adequately managed for hepatitis B prevention at birth, and there is no evidence that the low concentration of lamivudine in human milk leads to adverse reactions in breastfed infants. Therefore, breastfeeding may be considered in breast-feeding mothers being treated with lamivudine for HBV taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. Where there is maternal transmission of HBV, despite adequate prophylaxis, consideration should be given to discontinuing breastfeeding to reduce the risk of the emergence of lamivudine resistant mutants in the infant.
Fertility
Reproductive studies in animals have shown no effect on male or female fertility (see "Preclinical safety data").
Mitochondrial dysfunction
Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in infants exposed in utero and/or post-natally to nucleoside analogues (see "Special warnings and precautions for use").
Effects on ability to drive and use machines
Patients should be informed that malaise and fatigue have been reported during treatment with lamivudine. The clinical status of the patient and the adverse reaction profile of lamivudine should be borne in mind when considering the patient's ability to drive or operate machinery.
Undesirable effects
Summary of the safety profile
The incidence of adverse reactions and laboratory abnormalities (with the exception of elevations of ALT and CPK, see below) were similar between placebo and lamivudine treated patients. The most common adverse reactions reported were malaise and fatigue, respiratory tract infections, throat and tonsil discomfort, headache, abdominal discomfort and pain, nausea, vomiting and diarrhoea.
Tabulated list of adverse reactions
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), very rare (< 1/10,000) and not known (cannot be estimated from the available data).
The frequency categories assigned to the adverse reactions are mainly based on experience from clinical trials including a total of 1,171 patients with chronic hepatitis B receiving lamivudine at 100mg.

Blood and lymphatic system disorders	
Not known	Thrombocytopenia
Immune system disorders:	
Rare	Angioedema
Hepatobiliary disorders	
Very common	ALT elevations (see "Special warnings and precautions for use")
Exacerbations of hepatitis, primarily detected by serum ALT elevations, have been reported 'on-treatment' and following lamivudine withdrawal. Most events have been self-limited, however fatalities have been observed very rarely (see "Special warnings and precautions for use").	
Skin and subcutaneous tissue disorders	
Common	Rash, pruritus
Musculoskeletal and connective tissue disorders	
Common	Elevations of CPK
Common	Muscle disorders, including myalgia and cramps*
Not known	Rhabdomyolysis

* In Phase III studies frequency observed in the lamivudine treatment group was not greater than observed in the placebo group
Paediatric population
Based on limited data in children aged 2 to 17 years, there were no new safety issues identified compared to adults.
Other special populations
In patients with HIV infection, cases of pancreatitis and peripheral neuropathy (or paresthesia) have been reported. In patients with chronic hepatitis B there was no observed difference in incidence of these events between placebo and lamivudine treated patients.
Cases of lactic acidosis, sometimes fatal, 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 rare reports of lactic acidosis in patients receiving lamivudine for hepatitis B.
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
Pharmacodynamic properties
Pharmacotherapeutic group - Antivirals for systemic use, nucleoside and nucleotide reverse transcriptase inhibitors, ATC Code: J05AF05.
Lamivudine is an antiviral agent which is 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 alpha and beta. Furthermore, lamivudine-TP has little effect on mammalian cell DNA content.
In assays relating to potential substance 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.
Clinical experience
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 ≥ 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 mutant HBV, 41/82 (50 %) patients had improvement in liver inflammation and 40/56 (71 %) patients without YMDD mutant HBV had improvement. Improvement in bridging fibrosis occurred in 19/30 (63 %) patients without YMDD mutant and 22/44 (50 %) patients with the mutant. Five percent (3/56) of patients without the YMDD mutant and 13 % (11/82) of patients with YMDD mutant showed worsening in liver inflammation compared to pre-treatment. Progression to cirrhosis occurred in 4/68 (6 %) patients with the YMDD mutant, whereas no patients without the mutant 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 mutant status are summarised in Table 2.
Table 2: Efficacy results 5 years by YMDD status (Asian Study) NUCB3018

	Subjects, % (no.)			
YMDD mutant 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 mutant were those with ≥5 % YMDD mutant HBV at any annual time-point during the 5-year period. Patients categorised as non-YMDD mutant 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 mutant HBV, 18/39 (46 %) had improvements in necroinflammatory activity and 9/39 (23 %) had worsening. In patients without the mutant, 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, relapse following seroconversion can occur. In a long-term follow-up study of patients who had previously seroconverted and discontinued lamivudine, late virological relapse occurred in 39 % of the subjects. 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 3. 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 3: 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 mutant HBV, 14/22 (64 %) showed improvement in necroinflammatory score and 1/22 (5 %) patients worsened compared to pre-treatment. In patients with the mutant, 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 mutant HBV and impact on the treatment response
Lamivudine monotherapy results in the selection of YMDD mutant HBV in approximately 24 % of patients following one year of therapy, increasing to 69 % following 5 years of therapy. Development of YMDD mutant 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 "Special warnings and precautions for use").
In a double-blind study in CHB patients with YMDD mutant 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. Viral suppression was maintained (follow-on study NUC20917) with combined therapy during the second year of treatment to week 104 with patients having continued improvement in virologic and biochemical responses.
In a retrospective study to determine the factors associated with HBV DNA breakthrough, 159 Asian HBeAg-positive patients were treated with lamivudine and followed up for a median period of almost 30 months. Those with HBV DNA levels greater than 200 copies/mL at 6 months (24 weeks) of lamivudine therapy had a 60 % chance of developing the YMDD mutant compared with 8 % of those with HBV DNA levels less than 200 copies/mL at 24 weeks of lamivudine therapy. The risk for developing YMDD mutant was 63 % versus 13 % with a cut off of 1000 copies/ml (NUCB3009 and NUCB3018).
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 mutant HBV after 52 weeks treatment was higher (36 % - 64 %) in the liver transplant population than in the immunocompetent CHB patients (14 % - 32 %).
Forty patients (HBeAg negative or HBeAg positive) with either decompensated liver disease or recurrent HBV following liver transplantation and YMDD mutant were enrolled into an open label arm of study NUC20904. 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. This degree of viral suppression was maintained (follow-on study NUC20917) with combined therapy during the second year of treatment to week 104 and most patients had improved markers of liver function and continued to derive clinical benefit.
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 mutant HBV DNA (23/209, 11 %) compared to those without detectable YMDD mutant 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 mutant HBV was similar to that observed in adults, ranging from 19 % at week 52 up to 45 % in patients treated continuously for 24 months.
Pharmacokinetic properties
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 lamivudine 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.
Biotransformation
Lamivudine is predominately cleared by renal excretion of unchanged substance. The likelihood of metabolic substance interactions with lamivudine is low due to the small (5-10 %) extent of hepatic metabolism and the low plasma protein binding.
Elimination
The mean systemic clearance of lamivudine is approximately 0.3 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 "Posology and method of administration").
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 "Posology and method of administration").
Preclinical safety data
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 bacterial tests but, like many nucleoside analogues showed activity in an *in vitro* cytogenetic assay and the mouse lymphoma assay. 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.
Reproductive studies in animals have not shown evidence of teratogenicity and showed no effect on male or female fertility. Lamivudine induces early embryolethality when administered to pregnant rabbits at exposure levels comparable to those achieved in man, but not in the rat even at very high systemic exposures.
The results of long term carcinogenicity studies with lamivudine in rats and mice did not shown any carcinogenic potential.
PHARMACEUTICAL PARTICULARS
List of excipients
Tablet core:
Microcrystalline cellulose
Sodium starch glycolate
Magnesium stearate
Tablet film coat:
Hypromellose
Titanium dioxide
Macrogol 400
Polysorbate 80
Synthetic yellow and red iron oxides
Incompatibilities
Not applicable
Shelf life
The expiry date is indicated on the outer packaging.
Special precautions for storage
Store below 30ºC.
Nature and contents of container
Cartons containing 28 film-coated tablets in double foil blisters, laminated with polyvinyl chloride.
Manufacturer
Manufactured by:
GlaxoSmithKline Pharmaceuticals S.A., Poznan, Poland
Marketing Authorization Holder
Glaxo Group Ltd, Brentford, Middlesex, UK
ZEFFIX is a registered trademark of the GSK group of companies.

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THIS IS A MEDICAMENT
Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are the experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of reach of children.

Council of Arab Health Ministers, Union of Arab Pharmacists.