AUSTRALIAN PRODUCT INFORMATION

ZETLAM®

(lamivudine) film coated tablets

1 NAME OF THE MEDICINE

Lamivudine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ZETLAM tablet contains 100 mg of the active ingredient lamivudine.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

A peach, film-coated, capsule shaped, biconvex bevelled edge tablet debossed with "LN1" on one side and "M" on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ZETLAM (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 Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical Trials).

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults and adolescents 12* years and older: the recommended dosage of ZETLAM 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. For children requiring a dose of less than 100 mg daily, an alternate dose form containing 5 mg/mL Lamivudine oral solution is available in another brand.

* 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 Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical Trials).

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

To ensure administration of the entire dose, the tablet(s) should ideally be swallowed without crushing. For patients who are unable to swallow, the tablets may be crushed and 100% of the crushed tablets could be added to a small amount of semi-solid food or liquid, all of which should be consumed immediately (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Food reduces the C_{max} and extends the T_{max} but the amount of drug absorbed is not reduced. These changes to the pharmacokinetic parameters are not statistically or clinically significant (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Discontinuation of lamivudine 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 lamivudine.

Patient compliance should be monitored while on lamivudine therapy. If lamivudine is discontinued, patients should be periodically monitored for evidence of recurrent hepatitis (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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. For required doses less than 100 mg, an alternate dose form containing 5 mg/mL Lamivudine oral solution is available in another brand, see product information for dosage and administration instructions.

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

Hepatic impairment

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

4.3 CONTRAINDICATIONS

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 patients should be monitored regularly during treatment by a physician experienced in the management of chronic hepatitis B. Optimum duration of therapy has not been established.

During treatment, 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.

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.

The efficacy of lamivudine has not been established in patients not responding to alpha-interferon therapy.

Chronic hepatitis B is a highly variable condition and it is possible the patient may experience rebound during therapy (i.e. viral load increase or increase in liver enzyme levels) or other discordant results (e.g. increased HBV DNA and improved liver histology). Since there are no strong correlations between serological and histological markers of response, the decision on whether or not to continue lamivudine tablets therapy should be based on clinical status and serological marker trends rather than a single result.

Patients should be advised that therapy of chronic hepatitis B with lamivudine has not been proven to reduce the risk of transmission of hepatitis B virus to others through sexual contact or blood contamination and therefore, appropriate precautions should still be taken.

Pancreatitis and Neuropathy/Severe Hepatomegaly with Steatosis

In patients with HIV infection, cases of pancreatitis and peripheral neuropathy (or paraesthesia) have been reported although no relationship to treatment with lamivudine 150 mg and 300 mg tablets 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 100 mg daily treated patients.

Lactic Acidosis and Severe Hepatomegaly with Steatosis

Cases of lactic acidosis, usually associated with severe hepatomegaly and hepatic steatosis, including fatal cases have been reported with the use of antiretroviral nucleoside analogues alone or in combination, including lamivudine in the treatment of patients with HIV. A majority of these cases have been in women. Female sex, obesity and prolonged exposure nucleoside may be risk factors. Most of these reports have described patients receiving nucleoside analogues for the treatment of HIV infection, but there have been rare reports of lactic acidosis in patients receiving lamivudine for hepatitis B.

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 lamivudine to any patient with known risk factors for liver disease (other than hepatitis B); however, cases have also been reported in patients with no known risk factors. Treatment with lamivudine 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).

Cirrhotic Liver Disease/Hepatitis B Virus

Severe acute exacerbations of hepatitis have been reported in patients who have discontinued anti-hepatitis B therapy, including therapy with lamivudine. Hepatic function should be monitored closely in patients who discontinue anti-hepatitis B therapy. If appropriate, resumption of anti-hepatitis B therapy may be warranted.

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 (YMDD variant HBV) with reduced susceptibility to lamivudine have been identified during extended therapy. In a minority of cases this variant can lead to recurrent hepatitis, primarily detected by serum ALT elevations and re-emergence of HBV DNA. 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 Section 5.1 PHARMACODYNAMIC PROPERTIES). 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 of these variants is yet to be fully established.

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, in addition to the re-emergence of HBV DNA. Most events appear to have been self-limited. 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 compared with those receiving placebo. However, the proportion of patients who had post-treatment elevations associated with bilirubin elevations was low and similar in both treatment arms. For lamivudine-treated patients, the majority of post-treatment ALT elevations occurred between 8 and 12 weeks post-treatment.

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. If lamivudine tablets are discontinued or there is a loss of efficacy, some patients may experience clinical or laboratory evidence of recurrent hepatitis. For patients who develop evidence of recurrent hepatitis post-treatment, there are insufficient data on re-initiation of lamivudine treatment.

Exacerbations in patients with decompensated cirrhosis

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 clinical, virological and serological parameters associated with hepatitis B, for liver and renal function, and for antiviral response during treatment (at least every month). 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. 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.

For patients who develop evidence of recurrent hepatitis post-treatment, there are insufficient data on the benefits of re-initiation of lamivudine treatment.

Co-infection with HIV

Some chronic hepatitis B patients may be coinfected with HIV. The possibility of such coinfection should be considered prior to initiating lamivudine therapy.

There are no adequate clinical data on the treatment with lamivudine of patients co-infected with HIV and Hepatitis B virus. For the treatment of patients who are coinfected 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. Lamivudine 100 mg 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 and lamivudine/zidovudine combination tablets. 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.

Several serious adverse events have been reported with use of lamivudine in HIV infected patients. Reports of anaphylaxis, rhabdomyolysis and peripheral neuropathy have been rare (<1 in 1000).

The benefit of using lamivudine for treating chronic hepatitis B needs to be weighed against the potential compromise of a therapeutic option to subsequent progressive HIV and the possible emergence of drug resistant HIV.

Hematologic

Lamivudine use at higher doses in HIV disease has resulted in very rare occurrences of pure red cell aplasia. To date no definitive occurrences have been seen in hepatitis B patients at the recommended dose.

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 (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.

Delta Hepatitis or Hepatitis C

There are no clinical data on the efficacy of lamivudine 100 mg 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 100 mg. The standard recommended procedures for hepatitis B virus immunisation in infants should be followed.

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

Use in Hepatic Impairment

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION – Hepatic Impairment.

Use in 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 Section 4.2 DOSE AND METHOD OF ADMINISTRATION – Renal Impairment).

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.

Clinical resistance

In HBeAg positive or negative patients, 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 should be considered if serum HBV DNA remains detectable at or beyond 24 weeks of treatment.

Use in the Elderly

Clinical studies of lamivudine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. 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. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. In particular, because lamivudine is substantially excreted by the kidney and elderly patients are more likely to have decreased renal function, renal function should be monitored and dosage adjustments should be made accordingly (See section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Use in renal impairment).

Paediatric Use

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 section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical trials).

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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.

Effect of other agents on the pharmacokinetics of lamivudine

Lamivudine is a substrate of multidrug and toxin extrusion protein 1 (MATE1), MATE2-K and organic cation transporter 2 (OCT2) in vitro. Trimethoprim (an inhibitor of these drug transporters) when given in combination with sulphamethoxazole, has been shown to increase lamivudine plasma concentrations.

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 P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP), however due to its high bioavailability it is unlikely that these transporters play a significant role in the absorption of lamivudine. 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, BCRP or Pgp, MATE1, MATE2-K or 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, however lamivudine has low potential to affect the plasma concentrations of OCT1 and OCT2 substrates at therapeutic drug exposures.

Trimethoprim/Sulphamethoxazole 160 mg/800 mg

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.

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 Section 5.2 PHARMACOKINETIC PROPERTIES).

Alpha-interferon

Lamivudine has no pharmacokinetic interaction with alpha-interferon when the two drugs are concurrently administered.

Immunosuppressant drugs

There were no observed clinically significant adverse interactions in patients taking lamivudine concurrently with commonly used immunosuppressant drugs (e.g. cyclosporin A). However, formal interaction studies have not been performed.

Zalcitabine

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

Emtricitabine

Due to similarities, lamivudine should not be administered concomitantly with other cytidine analogues, such as emtricitabine. 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.

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).

Sorbitol

Co-administration 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 in lamivudine exposure in adults. When possible, avoid chronic co-administration of lamivudine with medicinal products containing sorbitol or other osmotic acting poly-alcohols or monosaccharide alcohols (e.g. xylitol, mannitol, lactitol, maltitol). Consider more frequent monitoring of HBV viral load when chronic coadministration cannot be avoided.

Drug-Herb interactions

Interactions with herbal products have not been established.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

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.

This reproductive study in rats has shown no effect on male or female fertility.

Use in Pregnancy (Risk Category B3)

Australian Pregnancy Category Definition of Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

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. Use in pregnancy should be considered only if the benefit outweighs the risk. Although the results of animal studies are not always predictive of human response, the findings in the rabbit suggest a potential risk of early embryonic loss. Consequently, lamivudine administration is not recommended during the first three months of pregnancy.

For patients who are being treated with lamivudine and subsequently become pregnant consideration should be given to the possibility of a recurrence of hepatitis on discontinuation of lamivudine (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Based on the limited data, it has not been established whether lamivudine can prevent the maternal-fetal 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.

Use in 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_{max}) of 16 to 19 times those observed at the clinical dosage.

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.

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

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 section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

4.7 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 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.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trial Information

Adults

In clinical studies of patients with chronic hepatitis B, lamivudine 100 mg 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 100 mg treated patients. The most common adverse events reported were malaise and fatigue, respiratory tract infections, throat and tonsil discomfort, 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

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

Children and Adolescents

In clinical studies of paediatric and adolescent patients with chronic hepatitis B, lamivudine 100 mg was well tolerated. The incidence of adverse events was similar between placebo and lamivudine 100 mg 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**.

Table 2 - Clinical adverse events almost certainly, probably or possibly related to lamivudine therapy occurring with an incidence of ≥3% in study NUC30903

	Treatment Group	
	Placebo N=96	**Lamivudine N=191**
Drug-Related Event	n (%)	n (%)
Abdominal Discomfort & Pain	8 (8)	8 (4)
Headache	5 (5)	11 (6)
Abnormal Liver Function Tests	4 (4)	7 (4)
Malaise & Fatigue	3 (3)	7 (4)
Nausea & Vomiting	3 (3)	6 (3)
Skin rashes	2 (2)	6 (3)
Pharyngitis	4 (4)	4 (2)
Feeding Problems	4 (4)	2 (1)
Diarrhoea	2 (2)	5 (3)

Adverse reactions are listed below by system organ class and frequency. Frequency categories are only assigned to those adverse reactions considered to be at least possibly causally related to lamivudine. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000) and very rare (<1/10,000).

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 of placebo groups was not taken into account. Adverse drug reactions identified through post-marketing surveillance were categorised as rare or very rare.

Hepatobiliary disorders

Very common: Elevations of ALT

Elevations in ALT were more common post-treatment in patients treated with lamivudine 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 lamivudine and placebo treated patients. The relationship of these recurrent hepatitis events to lamivudine treatment or to the previous underlying disease is uncertain (see Section 4.4 SPECIAL WARNINGS AND SPECIAL 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.

Musculoskeletal and connective tissue disorders

Common: Elevations of CPK, cramps

Metabolism

Very rare: Lactic acidosis

Immune system disorders

Rare: Angioedema

Skin and subcutaneous tissue disorders

Common: Rash, pruritus

Several serious adverse events were reported with lamivudine including lactic acidosis and severe hepatomegaly with steatosis, post-treatment exacerbations of hepatitis B, pancreatitis, and emergence of viral mutants associated with reduced drug susceptibility and diminished treatment response.

Post-Marketing Data

In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of lamivudine.

Blood and lymphatic system disorders

Unknown/Very rare: Thrombocytopenia, anaemia, neutropenia, pure red cell aplasia, lymphadenopathy, splenomegaly

Musculoskeletal and connective tissue disorders

Common: Muscle disorders, including myalgia, elevations of CPK and cramps

Unknown/Very rare: Rhabdomyolysis, arthralgia

Metabolism and nutrition disorders

Hyperlactataemia, hyperglycemia, lactic acidosis (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE), redistribution/accumulation of body fat. The incidence of this event is dependent on multiple factors including the particular antiretroviral drug combination.

Nervous system disorders

Headache, paraesthesia, peripheral neuropathy

Gastrointestinal disorders

Diarrhea, nausea, pancreatitis, rises in serum amylase, upper abdominal pain, vomiting

Skin and subcutaneous tissue disorders

Alopecia

General disorders and administration site conditions

Fatigue, fever, malaise

Respiratory

Abnormal breath sounds/wheezing

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.

In patients with HIV infection, cases of pancreatitis and peripheral neuropathy (or paresthesia) have been reported, although no relationship to treatment with lamivudine has been clearly established. 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, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of combination nucleoside analogue therapy in patients with HIV. There have been occasional reports of these adverse events in hepatitis B patients with decompensated liver disease, however the relation to treatment with lamivudine is unclear.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

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.

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 100 mg 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 100 mg 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 100 mg 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 100 mg patients (16%) than in placebo treated patients (4%) ($p<0.05$). Significantly more lamivudine 100 mg 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 100 mg 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 100 mg 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 100 mg once daily for 8 weeks followed by lamivudine 100 mg once daily plus interferon alpha monotherapy (10 MU 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 100 mg 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 100 mg 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 100 mg (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 lamivudine 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 100 mg daily has been administered prior to, during and post liver transplantation, to suppress existing or recurrent HBV. In some of these patients, lamivudine 100 mg 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 100 mg daily treatment. YMDD variant HBV was detected in a minority of chronic hepatitis B patients without decompensated liver disease treated with lamivudine 100 mg 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 lamivudine 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 100 mg daily was followed by a re-emergence of wild-type HBV which is sensitive to lamivudine 100 mg (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Therefore, despite the development of YMDD mutants, continuation of lamivudine 100 mg 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 3 mg/kg once daily to a maximum of 100 mg 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.

5.2 PHARMACOKINETIC PROPERTIES

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_{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 1-1.5 µg/mL and trough levels were 0.015 – 0.020 µg/mL.

The 100 mg 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 (AUC_{inf}) in the fed and fasted states. A reduction in C_{max} (about 10%) and delay in T_{max} (0.25 hrs) with the ingestion of a high fat meal were not statistically or clinically significant.

A separate bioavailability study was conducted comparing the generic Lamivudine 300 mg tablets with the originator Lamivudine 300 mg tablets. The generic and originator mean C_{max} for lamivudine was 2838.19 ng/mL and 3119.57 ng/mL respectively. The C_{max} point estimate for lamivudine was 0.9191 with the 90%

confidence interval between 0.8424 and 1.0028. The mean AUC_{∞} point estimate for lamivudine was 0.9910 with the 90% confidence interval between 0.9215 and 1.0657. The T_{max} for both the generic and originator tablets was 1.1 hours.

Administration of crushed tablets with a small amount of semi-solid food or liquid would not be expected to have an impact on the pharmaceutical quality, and would therefore not be expected to alter the clinical effect. This conclusion is based on physiochemical and pharmacokinetic data, assuming that the patient crushes and transfers 100% of the tablet and ingests immediately.

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.

Excretion

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 0.35 mg/kg twice daily, 3 mg/kg once daily, 1.5 mg/kg twice daily, or 4 mg/kg twice daily. Patients aged 13 to 17 years received lamivudine 100 mg once daily. Lamivudine was rapidly absorbed (T_{max} 0.5 to 1 hour). In general, both C_{max} and exposure (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 3 mg/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 100 mg/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 Section 4.2 DOSE AND METHOD OF 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 Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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 2000 mg/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.

Carcinogenicity

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 female 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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The tablets also contain the following inactive ingredients: microcrystalline cellulose, sodium starch glycollate Type A, magnesium stearate. The film coating contains propylene glycol with Opadry Complete Film Coating System 03H520008 Yellow (ID 107420).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

HDPE bottles with polypropylene caps of 28 and 84 tablets.

Some strengths, pack sizes and/or pack types may not be marketed.

** *ZETLAM is not commercially available as an oral solution.*

Australian Register of Therapeutic Goods (ARTG)

AUST R 180504 – ZETLAM lamivudine 100 mg tablet bottle

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

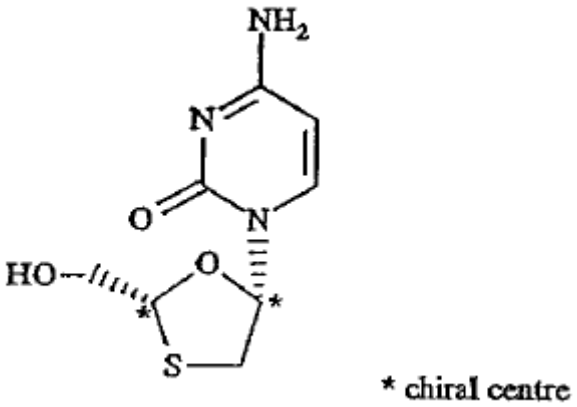
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Chemical name : Free base of (2*R*-Cis)-4-amino-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-(1H)-pyrimidin-2-one

Structural formula :



Molecular formula : $C_8H_{11}N_3O_3S$

Molecular weight : 229.26

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

CAS Number

134678-17-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

Level 1, 30 The Bond

30-34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

16/02/2012

10 DATE OF REVISION

05/02/2025

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes
4.4	Addition of information related to rebound and other discordant results during therapy. Addition of information to the 'Lactic Acidosis and sever hepatomegaly with steatosis' sub-section. Information related to discontinuation of therapy added in 'Exacerbations after treatment discontinuation' sub-section. 'Clinical, virological and serological' added as parameters to be monitored. Additional information added to 'Co-infection with HIV' sub-section.
4.5	Addition of 'Drug-Herb interactions' sub-section.
4.6	Information added to 'Use in Lactation' sub-section.
4.8	'Throat and tonsil discomfort' added to adverse events in 'Adults' sub-section. Information about serious adverse event reports added to 'Skin and subcutaneous tissue disorder' sub-section.
6.1	Update to proprietary ingredient number.

ZETLAM® is a Viatris company trade mark

ZETLAM_pi\Feb25/01