NEW ZEALAND DATA SHEET

ZETLAM

1. Product Name

ZETLAM, 100 mg, film-coated tablets.

2. Qualitative and Quantitative Composition

Each film-coated tablet contains 100 mg of lamivudine.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Peach coloured, film-coated, capsule shaped, biconvex bevelled edge tablet debossed with “LN1” on one side and “M” on the other side.

Do not halve tablet. Dose equivalence when the tablet is divided has not been established.

4. Clinical Particulars

4.1 Therapeutic indications

ZETLAM is indicated for the treatment of patients with chronic hepatitis B and evidence of hepatitis B virus (HBV) replication in adults and adolescents 12 years and older.

4.2 Dose and method of administration

Dose

The recommended dosage for adults and adolescents 12 years and older is 100 mg once daily.

Patient compliance should be monitored while on lamivudine therapy.

Discontinuation of ZETLAM may be considered in immunocompetent patients when HBeAg and/or HBsAg seroconversion occurs. Discontinuation may also be considered when loss of efficacy occurs, as indicated by recurrent signs of hepatitis.

If ZETLAM is discontinued, patients should be periodically monitored for evidence of recurrent hepatitis (see Section 4.4).

Discontinuation of treatment is not recommended in patients with decompensated liver disease. There are limited data regarding the maintenance of seroconversion long term after stopping treatment with lamivudine.

ZETLAM should be used in accordance with available official recommendations.

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.

Table 1: Dosing recommendations – adults and adolescents 12 years and older

Creatinine clearance (mL/min)	First Dose of Lamivudine*	Maintenance Dose Once Daily*
30 to < 50	100 mg	50 mg
15 to < 30	100 mg	25 mg
5 to < 15	35 mg	15 mg
< 5	35 mg	10 mg

* Refer to the respective lamivudine oral solution product datasheet for doses below 100 mg.

Data available in patients undergoing intermittent haemodialysis (less than or equal to 4hrs 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.

Method of administration

ZETLAM can be taken with or without food.

4.3 Contraindications

ZETLAM is contraindicated in patients with known hypersensitivity to lamivudine or to any ingredient of the preparation listed in section 6.1

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 by a physician experienced in the management of chronic hepatitis B.

If ZETLAM is discontinued or there is a loss of efficacy some patients may experience clinical or laboratory evidence of recurrent hepatitis. Exacerbation of hepatitis has primarily been detected by serum ALT elevations, in addition to the re-emergence of HBV DNA. See Table 3, Pharmacodynamic Properties, Clinical experience for more information regarding frequency of post treatment ALT elevations. Most events appear to have been self-limited. Fatalities are very rare and the causal relationship to discontinuation of lamivudine treatment is unknown.

If ZETLAM is discontinued, patients should be periodically monitored both clinically and by assessment of serum liver function tests (ALT and bilirubin levels), for at least four months for evidence of recurrent hepatitis; patients should then be followed as clinically indicated. For patients who develop evidence of recurrent hepatitis post-treatment, there are insufficient data on the benefits of re-initiation of ZETLAM treatment.

In patients with moderate to severe renal impairment, serum lamivudine concentrations (AUC) are increased due to decreased renal clearance, therefore the dose should be reduced for patients with a creatinine clearance of < 50 mL/minute (see Section 4.2).

Transplantation recipients and patients with advanced liver disease are at greater risk from active viral replication. Due to marginal liver function in these patients, hepatitis reactivation at discontinuation of lamivudine or loss of efficacy during treatment may induce severe and even fatal decompensation. It is recommended that these patients are monitored for parameters associated with hepatitis B, for liver and renal function, and for antiviral response during treatment. If treatment is discontinued for any reason, it is recommended that these patients are monitored for at least 6 months post cessation of treatment. Patients experiencing signs of hepatic insufficiency during or post-treatment should be monitored frequently, as appropriate.

There are limited data on the use of lamivudine in patients receiving concurrent immunosuppressive regimes, including cancer chemotherapy.

In HBeAg positive or negative patients, the development of YMDD (tyrosine-methionineaspartate-aspartate) mutant HBV may result in a diminished therapeutic response to lamivudine, indicated by a rise in HBV DNA and ALT from previous on-treatment levels. In order to reduce the risk of resistance in patients receiving lamivudine monotherapy, a switch to or addition of an alternative agent without cross-resistance to lamivudine should be considered if serum HBV DNA remains detectable at or beyond 24 weeks of treatment (see Section 5.1).

HBV viral subpopulations (YMDD variant HBV) with reduced susceptibility to lamivudine have been identified during extended therapy (see Section 5.1). In a minority of cases this variant can lead to recurrent hepatitis.

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.

There is limited 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.

4.5 Interaction with other medicines and other forms of interaction

The likelihood of metabolic interactions is low due to limited metabolism and plasma protein binding and almost complete renal elimination of unchanged medicine.

Lamivudine is predominantly eliminated by active organic cationic secretion. The possibility of interactions with other medicines 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 medicines (e.g. ranitidine, cimetidine) are eliminated only in part by this mechanism and were shown not to interact with lamivudine.

Medicines shown to be predominantly excreted either via the active organic anionic pathway, or by glomerular filtration are unlikely to yield clinically significant interactions with lamivudine.

Interaction relevant to 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 Section 5.2).

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.

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 of 14%, 32%, and 36% in lamivudine exposure (AUC_{∞}) and 28%, 52%, and 55% in the C_{max} of lamivudine in adults. When possible, avoid use of ZETLAM with sorbitol-containing medicines or consider more frequent monitoring of HBV viral load when chronic co-administration cannot be avoided.

Lamivudine has no pharmacokinetic interaction with α-interferon when the two medicines are concurrently administered. There were no observed clinically significant adverse interactions in patients taking lamivudine concurrently with commonly used immunosuppressant medicines (e.g. ciclosporin A). However, formal interaction studies have not been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy

Lamivudine has been evaluated in the Antiretroviral Pregnancy Registry in over 11,000 women during pregnancy and postpartum. Less than 1% of these women have been treated for HBV, whereas the majority was treated for HIV at higher doses and with other concomitant HIV medications. Available human data from the Antiretroviral Pregnancy Registry do not show an increased risk of major birth defects for lamivudine compared to the background rate (see Section 5.1). However, there are no adequate and well controlled trials in pregnant women and the safe use of lamivudine in human pregnancy has not been established.

Studies in humans have confirmed that lamivudine crosses the placenta.

Use in pregnancy should be considered only if the benefit outweighs the risk. Although the results of animal studies (see Section 5.3) are not always predictive of human response, there was no evidence of teratogenicity in animals but, findings in rabbit suggest a potential risk of early embryonic loss that was not observed in the rat.

For patients who are being treated with ZETLAM and subsequently become pregnant, consideration should be given to the possibility of a recurrence of hepatitis on discontinuation of ZETLAM (see Section 4.4).

Breast-feeding

Following repeat oral administration of either 150 mg or 300 mg lamivudine twice daily, lamivudine was excreted in human breast milk (0.5 to 8.2 micrograms/mL) at similar concentrations to those found in serum. In other studies, following repeat oral administration of 150 mg lamivudine twice daily the breast milk:maternal plasma ratio ranged between 0.6 and 3.3. Lamivudine median infant serum concentrations ranged between 18 and 28 nanogram/mL and were not detectable in one of the studies (assay sensitivity 7 nanogram/mL). The clinical relevance of this finding is unknown.

Data from animal studies in which neonatal rats received lamivudine at much higher concentrations via maternal milk suggest that the concentrations of lamivudine in human breast milk are unlikely to produce toxicity in breast fed infants.

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 breast-feeding or to discontinue/abstain from lamivudine therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

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

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 would not be predicted from the pharmacology of the medicine.

4.8 Undesirable effects

Summary of the safety profile

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

Table 2: Adverse events placebo vs. lamivudine

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

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

The incidence of laboratory abnormalities in chronic hepatitis B patients were similar in the lamivudine and placebo treated groups, with the exception of ALT elevations which were more common post-treatment in patients treated with lamivudine. In controlled trials 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).

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, < 1/10), uncommon (≥ 1/1000, < 1/100), rare (≥ 1/10,000, < 1/1000) and very rare (< 1/10,000).

The frequency categories assigned to the adverse reactions below are estimates: for most events, suitable data for calculating incidence are not available. Very common and common adverse drug reaction frequency categories were determined from clinical trial data and the background incidence in placebo groups was not taken into account. Adverse drug reactions identified through post-marketing surveillance were categorised as rare or very rare.

Clinical trial data

Hepato-biliary 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).

Skin and subcutaneous tissue disorders

Common: Rash

Musculoskeletal, connective tissue and bone disorders

Common: Elevations of CPK

Observed during clinical practice

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

Blood and the lymphatic system disorders

Very Rare: Thrombocytopenia

Musculoskeletal, connective tissue and bone disorders

Common: Muscle disorders, including myalgia and cramps.

Very Rare: Rhabdomyolysis

Other special populations

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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

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 further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: nucleoside analogue, ATC code: J05AF05.

Mechanism of action

Lamivudine is an antiviral agent which is highly active against hepatitis B virus (HBV) in all cell lines tested and in experimentally infected animals.

Pharmacodynamic effects

Lamivudine is metabolised by both infected and uninfected cells to the triphosphate (TP) derivative which is the active form of the parent compound. The intracellular half-life of the triphosphate in hepatocytes is 17-19 hours *in vitro*. Lamivudine-TP acts as a substrate for the HBV viral polymerase. The formation of further viral DNA is blocked by incorporation of lamivudine-TP into the chain and subsequent chain termination.

Lamivudine-TP does not interfere with normal cellular deoxynucleotide metabolism. It is also only a weak inhibitor of mammalian DNA polymerases α and β. Furthermore, lamivudine-TP has little effect on mammalian cell DNA content.

In assays relating to potential drug effects on mitochondrial structure and DNA content and function, lamivudine lacked appreciable toxic effects.

It has a very low potential to decrease mitochondrial DNA content, is not permanently incorporated into mitochondrial DNA, and does not act as an inhibitor of mitochondrial DNA polymerase γ.

Clinical efficacy and safety

Lamivudine has potent anti-viral activity *in vivo*, rapidly suppressing HBV replication following initiation of treatment, resulting in continued HBV suppression, normalisation of serum aminotransferase, significant reductions in liver necro-inflammatory activity, reduced progression of fibrosis and increased HBeAg seroconversion. Lamivudine has been administered to chronic hepatitis B patients for up to four years in clinical studies. Similar results have been seen in patients regardless of ethnic origin.

In controlled studies in over 800 HBeAg positive patients, treatment with lamivudine for 1 year significantly suppressed HBV DNA replication (34-57% of patients), normalised ALT levels (40-72% of patients), induced HBeAg seroconversion (HBeAg and HBV DNA loss with HBeAb detection, 16-18% of patients), improved histology (38-52% of patients), and reduced progression of fibrosis (3-17% of patients) and progression to cirrhosis (1.8% of patients).

The HBeAg seroconversion was maintained in 81% (34/42) of patients off drug followed for approximately 2 years. In addition, HBsAg seroconversion was achieved in 21% (9/42) patients.

In HBeAg positive patients who had not experienced HBeAg seroconversion in 1-year controlled studies and were subsequently treated with 2 years of lamivudine, 77/128 (60%) had improvement in liver inflammation and 26/51 (51%) had improvement in bridging fibrosis.

In an additional study, after four years of lamivudine therapy HBeAg seroconversion (HBeAg loss and HBeAb detection) was seen in 47% (27/58) patients (59% [24/41] of patients with abnormal baseline ALT).

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 patients followed for up to 16 weeks after discontinuation of treatment, post-treatment ALT elevations were observed more frequently in patients who had received lamivudine than in patients who had received placebo. A comparison of 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.

Table 3: Post-treatment ALT elevations in 2 Placebo-controlled studies in adults with No-active-treatment follow-up.

Abnormal value	Patients with ALT elevation/ Patients with observations[#]	
	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.

In a placebo controlled study of 286 hepatitis B patients aged 2 to 17 years, 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]). Normalisation of serum ALT was more frequent in patients treated with lamivudine compared with placebo (55% [100/183] vs 13% [11/88]). 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.

HBV viral sub-populations with reduced susceptibility to lamivudine *in vitro* have been identified. These HBV variants (YMDD variant HBV) are also found in hepatitis B patients who experience a return of detectable serum HBV DNA levels whilst on lamivudine treatment. The incidence of YMDD variant HBV (see Section 4.4), as detected by polymerase chain reaction, increases with duration of treatment; 20% after 1 year, 53% after 3 years, 70% after 4 years and may be higher in immunocompromised patients.

Despite the emergence of YMDD variant 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, the majority of patients with YMDD variant HBV maintained serum HBV DNA and ALT levels lower than their pre-treatment values, and a proportion experienced HbeAg seroconversion. The adverse event profile is similar for patients with or without YMDD variant HBV.

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 Section 4.4).

In patients with HBeAg negative chronic hepatitis B, the efficacy of lamivudine was similar to those infected with wild type HBV (e.g. 71% of patients with HBV DNA suppression, 67% with ALT normalisation and 38% with Knodell HAI-score improvement at one year on treatment). If therapy

with lamivudine is stopped after 1 year of treatment, the majority of patients with HBeAg negative chronic hepatitis B have a return of viral replication. Limited data indicate that extended lamivudine treatment (2 years) maintains HBV DNA suppression and ALT normalisation in this patient population. The incidence of serious adverse events at anytime during and post-treatment was low and similar in patients with HBeAg negative chronic hepatitis B with or without YMDD variant HBV.

In non-controlled studies in liver transplant patients in which 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 a one year survival rate of 76-100%. These studies were not placebo-controlled as this was regarded inappropriate in patients with decompensated liver disease.

As anticipated due to the concomitant immunosuppression, the rate of emergence of YMDD variant HBV after 52 weeks treatment was higher (36% - 64%) in liver transplant patients compared with immunocompetent chronic hepatitis B patients (14% - 32%). Studies provide evidence however that the emergence of YMDD variant is not consistently associated with hepatic disease progression and that the majority of patients may continue to benefit from continued lamivudine therapy.

Studies of monotherapy with lamivudine compared to α-interferon alone or in combination for treatment of chronic hepatitis B patients, showed no significant difference in histologic response or HBeAg seroconversion rates between the treatment groups. The safety profile of lamivudine was superior to the α interferon containing treatment regimens.

There is no clinical data on the efficacy of lamivudine in patients co-infected with Delta hepatitis.

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

5.2 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 microgram/mL and trough levels were 0.015-0.020 microgram/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 significantly, therefore ZETLAM 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 enters 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 drug. The likelihood of metabolic drug interactions with lamivudine is low due to the small (5-10%) extent of hepatic metabolism and the low plasma protein binding.

Effect of other agents on the pharmacokinetics of lamivudine

Lamivudine is a substrate of MATE1, MATE2-K and OCT2 in vitro. Trimethoprim (an inhibitor of these drug transporters) when given in combination with sulphamethoxazole, has been shown to increase lamivudine plasma concentrations (see Section 4.5)

Lamivudine is a substrate of the hepatic uptake transporter OCT1. As hepatic elimination plays a minor role in the clearance of lamivudine, drug interactions due to inhibition of OCT1 are unlikely to be of clinical significance.

Lamivudine is an *in vitro* substrate of Pgp and BCRP, however due to its high bioavailability it is unlikely that these transporters play a significant role in the absorption of lamivudine. Therefore co-administration of drugs that are inhibitors of these efflux transporters is unlikely to affect the disposition and elimination of lamivudine.

Effect of lamivudine on the pharmacokinetics of other agents

In vitro, lamivudine demonstrates no or weak inhibition of the drug transporters organic anion transporter 1B1 (OATP1B1), OATP1B3, breast cancer resistance protein (BCRP) or P-glycoprotein (Pgp), multidrug and toxin extrusion protein 1 (MATE1), MATE2-K or organic cation transporter 3 (OCT3). Lamivudine is therefore not expected to affect the plasma concentrations of drugs that are substrates of these drug transporters.

Lamivudine is an inhibitor of OCT1 and OCT2 in vitro with IC50 values of 17 and 33 uM, respectively, however lamivudine has low potential to affect the plasma concentrations of OCT1 and OCT2 substrates at therapeutic drug exposures (up to 300 mg which is three times higher than the recommended maximum dose of HBV).

Elimination

The mean systemic clearance of lamivudine is approximately 0.3 L/h/kg. The observed half-life of elimination is 5 to 7 hours. The majority of lamivudine is excreted unchanged in the urine via glomerular filtration and active secretion (organic cationic transport system).

Renal clearance accounts for about 70% of lamivudine elimination.

Special populations

Renal impairment

Studies in patients with renal impairment show lamivudine elimination is affected by renal dysfunction. Dose reduction in patients with a creatinine clearance of <50 mL/min is necessary (see Section 4.2).

Hepatic impairment

A study in hepatically impaired patients (non-HIV and non-HBV infected) showed lamivudine is well tolerated in this patient group with no changes in laboratory parameters or the adverse event profile of lamivudine. The pharmacokinetics of lamivudine are unaffected by hepatic impairment.

Limited data in patients undergoing liver transplantation show that impairment of hepatic function does not impact significantly on the pharmacokinetics of lamivudine unless accompanied by renal dysfunction.

Elderly

In elderly patients the pharmacokinetic profile of lamivudine suggests that normal ageing with accompanying renal decline has no clinically significant effect on lamivudine exposure, except in patients with creatinine clearance of <50 mL/min. (see Section 4.2).

Pregnancy

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

Lamivudine concentrations in infant serum at birth were similar to those in maternal and cord serum at delivery.

Paediatric population

In paediatric patients lamivudine pharmacokinetics are generally similar to adults. However, weight-corrected oral clearances were higher in children resulting in lower AUCs than adults. Age-stratified oral clearance was highest at age 2 and declined from 2 to 12 years, where values were then similar to those seen in adults. A dose of 3 mg/kg given once daily produced a steady-state lamivudine AUC similar to that associated with a dose of 100 mg/day in adults. The recommended dose for children from 2 to eleven years of age is 3 mg/kg once daily up to a maximum of 100 mg daily which will provide comparable exposure to the adult recommended dose (100 mg once a day). There are limited pharmacokinetic data for patients less than 2 years of age.

5.3 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.

The results of long term carcinogenicity studies with lamivudine in rats and mice did not show any carcinogenic potential.

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

6. Pharmaceutical Particulars

6.1 List of excipients

Tablet core:

- Microcrystalline cellulose
- Sodium starch glycollate
- Magnesium stearate

Tablet film coat:

- Hypromellose
- Titanium dioxide
- Propylene glycol
- Iron oxide yellow (E172)
- Iron oxide red (E172)

ZETLAM tablets are lactose and gluten free.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years – Bottle of 60 tablets and all blister packs

3 years – Bottle of 28 tablets

6.4 Special precautions for storage

Store at or below 30°C.

6.5 Nature and contents of container

HDPE bottle with a PP cap. Pack-sizes of 28 or 60 film-coated tablets.

Blister pack, PVdC/PVC/Al. Pack-sizes of 28 or 60 film-coated tablets.

Not all pack types and sizes may be marketed.

6.6 Special precautions for disposal and other handling

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Mylan New Zealand Ltd
PO Box 11183
Ellerslie
AUCKLAND
Telephone 09-579-2792

9. Date of First Approval

15 September 2011

10. Date of Revision of the Text

21 January 2020

Summary of Changes:

Section	Change
6.3	Shelf life