AUSTRALIAN PRODUCT INFORMATION

LAMIVUDINE ALPHAPHARM

Lamivudine film-coated tablets

1 NAME OF THE MEDICINE

Lamivudine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

LAMIVUDINE ALPHAPHARM film-coated tablets contain 150 mg or 300 mg lamivudine as the active ingredient.

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

3 PHARMACEUTICAL FORM

LAMIVUDINE ALPHAPHARM 150 mg film-coated tablets:	White to off-white film-coated, capsule shaped, biconvex tablet debossed with "M105" on one side of the tablet and a score line on the other side.
LAMIVUDINE ALPHAPHARM 300 mg film-coated tablets:	White to off-white, film-coated, oval shaped, biconvex tablet debossed with "M300" on one side of the tablet and blank on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Lamivudine tablets in combination with other antiretroviral agents is indicated for the treatment of HIV infected adults and children.

4.2 DOSE AND METHOD OF ADMINISTRATION

Food reduces the C_{max} and extends the T_{max} but the amount of drug absorbed is not reduced. The clinical significance of this is not known (see **Section 5.2 PHARMACOKINETIC PROPERTIES**).

Clinical studies indicate that lamivudine should be used in combination with other antiretroviral therapies. In controlled trials in adults, lamivudine was used in combination with zidovudine 200 mg tds (see **Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials**).

Since accurate dosing cannot be achieved with this formulation, dosing according to weight bands is recommended for scored tablets. This dosing regimen for paediatric patients weighing 14 - 30 kg is based primarily on pharmacokinetic modelling. Therefore monitoring of efficacy and safety is necessary in these patients. More accurate dosing can be achieved with oral solution of lamivudine (see Section **5.2 PHARMACOKINETIC PROPERTIES - Pharmacokinetics in children**).

To ensure administration of the entire recommended dose, the tablet(s) should be swallowed whole and not divided or crushed. If the patient is unable to swallow whole tablets, 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**). Alternatively, lamivudine is available as an oral solution in another brand.

Adults, Adolescents and Children weighing at least 25 kg

The recommended dose of lamivudine is 150 mg twice daily. Alternatively, it may be administered as 300 mg once daily in patients who may benefit from a once daily regimen (see **Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials**).

Children

Children less than three months of age:

The limited data available are insufficient to propose specific dosage recommendations (see **Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials** and **Section 5.2 PHARMACOKINETIC PROPERTIES**).

Children weighing 14 to < 20 kg:

The recommended total daily dose of lamivudine is 150 mg. This may be administered as either one-half of a 150 mg scored tablet (75 mg) twice daily or one whole 150 mg tablet once daily.

Children weighing ≥ 20 kg to < 25 kg:

The recommended total daily dose of lamivudine is 225 mg. This may be administered as either one-half of a 150 mg scored tablet (75 mg) in the morning and one whole 150 mg tablet in the evening, or one and a half 150 mg scored tablets (225 mg) once daily.

Children weighing at least 25 kg:

The adult dosage of 150 mg twice daily or 300 mg once daily should be taken. Lamivudine is also available as an oral solution in another brand.

Data regarding the efficacy of once-daily dosing in paediatric population is limited to patients who transitioned from twice-daily to once-daily dosing after 36 weeks of treatment (see **Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials**).

Renal Impairment

Lamivudine plasma concentrations (AUC) are increased in patients with moderate to severe renal impairment due to decreased clearance. The dose should therefore be adjusted (see **Table 1 and 2**). There are no data available on the use of lamivudine in children with renal impairment. The same percentage reduction in the adult dose is recommended for children with renal impairment. A reduction in the dose and/or an increase in the dosing interval should be considered in children aged at least three months and weighing less than 25 kg.

Table 1 – Dosing recommendations for patients with renal impairment – Adults, Adolescents and Children weighing at least 25 kg *

Creatinine clearance (mL/min)	First Dose	Maintenance Dose
30 to less than 50	150 mg	150 mg once daily
15 to less than 30	150 mg	100 mg once daily
5 to less than 15	150 mg	50 mg once daily
less than 5	50 mg	25 mg once daily

Table 2 – Dosing recommendations for patients with renal impairment – Children ≥ 3 months and weighing less than 25 kg *

Creatinine clearance (mL/min)	First Dose	Maintenance Dose
30 to less than 50	5 mg/kg	5 mg/kg once daily
15 to less than 30	5 mg/kg	3.25 mg/kg once daily
5 to less than 15	5 mg/kg	1.63 mg/kg once daily
less than 5	1.63 mg/kg	0.88 mg/kg once daily

*** If required, an oral solution is available in another brand for more practical dosing.**

Intermittent dialysis is unlikely to require further dose modification from that defined by creatinine clearance.

Hepatic Impairment

Data obtained in patients with moderate to severe hepatic impairment shows that lamivudine pharmacokinetics are not significantly affected by hepatic dysfunction. Based on these data, no dose adjustment is necessary in patients with moderate or severe 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

Lamivudine is not recommended for use as monotherapy.

Transmission of infection
While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines

Patients receiving lamivudine or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close clinical observation by physicians experienced in the treatment of patients with associated HIV diseases.

Use with Caution in the Following Circumstances

Pancreatitis

Pancreatitis has been observed in some patients receiving lamivudine. However it is unclear whether this was due to treatment with the medicinal product or to the underlying HIV disease. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of lamivudine until diagnosis of pancreatitis is excluded.

Pancreatitis in Paediatric Patients

In paediatric patients with a history of pancreatitis or other significant risk factors for the development of pancreatitis, lamivudine should be used with extreme caution and only if there is no satisfactory alternative therapy. Treatment with lamivudine should be stopped immediately if clinical signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur [see **Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**].

Cirrhotic liver disease/Hepatitis B virus

Clinical trial and marketed use of lamivudine have shown that some patients with chronic hepatitis B virus (HBV) disease may experience clinical or laboratory evidence of recurrent hepatitis upon discontinuation of lamivudine, which may have more severe consequences in patients with decompensated liver disease. If lamivudine is discontinued in a patient with HIV and HBV coinfection, periodic monitoring of both liver function tests and markers of HBV replication should be considered.

Fat loss or fat gain

Fat loss or fat gain has been reported during combination antiretroviral therapy. The long term consequences of these events are currently unknown. A causal relationship has not been established.

Serum lipids and blood glucose

Serum lipid and blood glucose levels may increase during antiretroviral therapy. Disease control and lifestyle changes may also be contributing factors. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

Lactic acidosis and severe hepatomegaly with steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues either alone or in combination, including lamivudine. A majority of these cases have been in women.

Clinical features which may be indicative of the development of lactic acidosis include generalised weakness, anorexia, and sudden unexplained weight loss, gastrointestinal symptoms and respiratory symptoms (dyspnoea and tachypnoea).

Caution should be exercised when administering lamivudine to any patient, and particularly to those with known risk factors for liver disease. Treatment with lamivudine should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis with or without hepatitis (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Immune Reconstitution Syndrome

In HIV-infected patients with severe immune deficiency at the time of initiation of anti-retroviral therapy (ART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of ART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and *Pneumocystis jiroveci (P. carinii)* pneumonia. Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary. Autoimmune disorders (such as Graves' disease, polymyositis and Guillain-Barre syndrome) have also been reported to occur in the setting of immune reconstitution, however the time to onset is more variable, and can occur many months after initiation of treatment and sometimes can be an atypical presentation.

Osteonecrosis

Although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

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, the terminal plasma half-life of lamivudine exposure is increased due to decreased clearance. The dose should be adjusted (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION**).

Use in the Elderly

No data available.

Paediatric Use

Children who at any time received lamivudine oral solution concomitantly with other antiretroviral oral solutions in clinical trials experienced lower rates of virological suppression, had lower plasma lamivudine exposure and developed viral resistance more frequently than children receiving tablets (see **Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials** and **Section 5.2 PHARMACOKINETIC PROPERTIES**).

An all-tablet antiretroviral regimen should be used when possible. Lamivudine oral solution given concomitantly with sorbitol-containing medicines should be used only when the benefits of treatment outweigh possible risks including lower virological suppression. Consider more frequent monitoring of HIV-1 viral load when lamivudine is used with chronically-administered, sorbitol-containing medicines (see **Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**).

Effects on Laboratory Tests

See **Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).**

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The likelihood of 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.

Coadministration of sorbitol solution (3.2 g, 10.2 g, 13.4 g) with a single 300 mg dose of lamivudine oral solution resulted in dose-dependent decreases (90% CI) of 14% (9 - 20%), 32% (28 - 37%), and 36% (32 - 41%) in lamivudine exposure (AUC∞) and 28% (20 - 34%), 52% (47 - 57%), and 55% (50 - 59%) in the C_{max} of lamivudine in adults. When possible, avoid use of lamivudine with sorbitol-containing medicines or consider more frequent monitoring of HIV-1 viral load when chronic coadministration cannot be avoided (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

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).

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) has been shown to increase lamivudine plasma concentrations, however this interaction is not considered clinically significant as no dose adjustment of lamivudine is needed.

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 a 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.

Interactions relevant to lamivudine

Changes in zidovudine plasma levels when co-administered with lamivudine were not statistically significant. Zidovudine has no effect on the pharmacokinetics of lamivudine (see **Section 5.2 PHARMACOKINETIC PROPERTIES**).

Administration of trimethoprim, as trimethoprim/sulfamethoxazole 160 mg/800 mg increased lamivudine exposure by about 40%. However, unless the patient already 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. The effect of co- administration of lamivudine with higher doses of co-trimoxazole for the treatment of *Pneumocystis carinii* pneumonia and toxoplasmosis has not been studied.

In *in vitro* studies, ciprofloxacin, pentamidine and ganciclovir reduced the anti-HIV activity of lamivudine. The clinical significance of this is not known.

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.

Lamivudine may inhibit the intracellular phosphorylation of emtricitabine when the two medicinal products are used concurrently. Additionally, the mechanism of viral resistance for both lamivudine and emtricitabine is mediated via mutation of the same viral reverse transcriptase gene (M184V) and therefore the therapeutic efficacy of these drugs in combination therapy may be limited. Lamivudine is not recommended for use in combination with emtricitabine or emtricitabine-containing fixed dose combinations.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No evidence of impaired fertility was seen in rats with exposures (based on C_{max}) up to 70 times those observed at the clinical dosage.

Use in Pregnancy

(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.

The Antiretroviral Pregnancy Registry has received reports of over 11,000 exposures to lamivudine during pregnancy resulting in live birth. These consist of over 4,200 exposures during the first trimester, over 6, 900 exposures during the second/third trimester and included 135 and 198 birth defects respectively. The prevalence (95% CI) of defects in the first trimester was 3.2% (2.6, 3.7%) and in the second/third trimester, 2.8% (2.4, 3.2%). Among pregnant women in the reference population, the background rate of birth defects is 2.7%.

Studies in humans have confirmed that lamivudine crosses the placenta. Use in pregnancy should be considered only if the benefit outweighs the risk.

No evidence of teratogenicity was observed in rats and rabbits with exposure (based on C_{max}) up to 40 and 36 times respectively those observed in humans at the clinical dosage. However, embryolethality was increased with consequent reduction in litter size in rabbits at exposures (based on both C_{max} and AUC values) of less than those observed at the clinical dosage of 150 mg bd (approximately 4 mg/kg).

Lamivudine crossed the placenta in rats and rabbits. 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.

There have been reports of mild, transient elevations in serum lactate levels, which may be due to mitochondrial dysfunction, in neonates and infants exposed *in utero* or peri-partum to nucleoside reverse transcriptase inhibitors (NRTIs). The clinical relevance of transient elevations in serum lactate is unknown. There have also been very rare reports of developmental delay, seizures and other neurological disease. However, a causal relationship between these events and NRTI exposure *in utero* or peri-partum has not been established. These findings do not affect current recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Use in Lactation

Health experts recommend that where possible women infected with HIV do not breast feed their infants in order to avoid the transmission of HIV. In settings where formula feeding is not feasible, local official lactation and treatment guidelines should be followed when considering breast feeding during antiretroviral therapy.

A study in lactating rats showed that the concentration of lamivudine in milk, was more than four times higher than that in maternal plasma. In a study following repeat oral dose of either 150 mg lamivudine twice daily (given in combination with 300 mg zidovudine twice daily) 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 maternal serum.

In other studies following repeat oral dose of 150 mg lamivudine twice daily (given either in combination with 300 mg zidovudine or as lamivudine/zidovudine or abacavir/lamivudine/zidovudine) the breast milk:maternal plasma ratio ranged between 0.6 and 3.3. Lamivudine median infant serum concentrations ranged between 18 and 28 ng/mL and were not detectable in one of the studies (assay sensitivity 7 ng/mL). Intracellular lamivudine triphosphate (active metabolite of lamivudine) levels in the breastfed infants were not measured therefore the clinical relevance of the serum concentrations of the parent compound measured is unknown.

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 both lamivudine and zidovudine should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Table 3 lists all adverse events, occurring at an incidence of 5% or more, reported in controlled pivotal clinical trials in adults, irrespective of the investigator's assessment of the possible relationship to the study drug.

Table 3 – Common adverse events (frequency ≥5.0%) reported in four pivotal, controlled clinical trials in adults

	ZDV	ZDV + LAM (150)	ZDV + LAM (300)	ZDV + DDC (0.75)
n =	**230**	**251**	**318**	**86**
BLOOD AND LYMPHATIC				
Lymphatic signs & symptoms	4.8	9.2	7.2	11.6
Decreased white cells	3.5	5.2	5.0	9.3
EAR, NOSE AND THROAT				
Throat & tonsil discomfort & pain	9.6	9.2	11.6	14.0
Viral ear, nose & throat infection	7.4	9.6	6.9	12.8
Ear, nose & throat infection	7.0	10.8	11.3	12.8
Sinusitis	6.5	6.8	7.2	4.7
Upper respiratory inflammation	1.7	5.2	3.8	3.5
GASTROINTESTINAL				
Abdominal discomfort & pain	9.1	8.4	11.3	8.1
Fungal gastrointestinal infection	5.2	6.4	7.5	14.0
Gastrointestinal discomfort & pain	5.2	7.2	4.1	5.8
Gaseous symptoms	2.6	5.2	3.1	2.3
LOWER RESPIRATORY				
Bronchitis	4.8	10.0	4.7	5.8
Breathing disorders	3.5	5.6	4.1	3.5
MUSCULOSKELETAL				
Musculoskeletal pain	9.6	12.0	13.5	22.1
Muscle pain	5.7	8.4	3.5	11.6
NEUROLOGY				
Headache	27.0	35.1	28.9	33.7
Neuropathy	10.0	12.4	8.5	23.3
Sleep disorders	7.0	10.8	11.6	8.1
Dizziness	3.9	10.4	6.0	9.3
NON-SITE SPECIFIC				
Viral infection	4.3	7.6	6.6	20.9
SKIN				
Sweating	7.0	7.6	6.3	7.0
Fungal skin infection	6.1	5.6	4.1	7.0
Acne & folliculitis	3.9	6.8	3.5	11.6
Viral skin infection	3.5	5.2	4.7	7.0

Common laboratory abnormalities observed during therapy are listed in **Table 4**.

Table 4 – Frequencies of common laboratory abnormalities in 4 pivotal, controlled clinical trials in adults*

Test (Abnormal Level)	Lamivudine 150mg b.i.d. Plus zidovudine % (n)	Zidovudine % (n)
Neutropenia (ANC < 750/mm^3)	7.2% (237)	5.4% (222)
Anaemia (Hb < 8.0 g/dL)	2.9% (241)	1.8% (218)
Thrombocytopenia (platelets < 50,000/mm^3)	0.4% (240)	1.3% (223)
ALT (>5.0 x ULN)	3.7% (241)	3.6% (224)
AST (>5.0 x ULN)	1.7% (241)	1.8% (223)
Bilirubin (>2.5 ULN)	0.8% (241)	0.4% (220)
Amylase (>2.0 ULN)	4.2% (72)	1.5% (133)

ULN = Upper Limit of Normal ANC = Absolute Neutrophil
Count n = Number of patients assessed

Frequencies of these laboratory abnormalities were higher in patients with mild laboratory abnormalities at baseline.

Lamivudine appears to be well tolerated and most serious adverse events reported in clinical trials are not considered to be drug related. Adverse reactions from the 4 pivotal studies in adult patients receiving the recommended dose of lamivudine (150 mg bd) in combination with zidovudine 600 mg/day are included in **Table 5** together with serious adverse reactions reported in large scale open studies.

With many of these adverse reactions it is unclear whether they are drug -related or are a result of the underlying disease.

Table 5 – Adverse drug reactions reported in controlled trials and open studies

Adverse reactions reported in controlled clinical trials – (n = 251) Lamivudine 150 mg bd + zidovudine 600 mg/day	**Serious adverse reactions reported in open studies (n = 17,572), Lamivudine 300mg bd (n = 10,575), Lamivudine 150 bd (n = 6997), generally in combination with other antiretroviral therapy**
Non-site specific	**Non-site specific**
Very common Malaise and fatigue *Common* Fever	*Rare* Malaise and fatigue, fever
Blood and Lymphatic	**Blood and Lymphatic**
Common Anaemia, decreased white cells	*Uncommon* Decreased white cells *Rare* Anaemia Thrombocytopenia
Neurological	**Neurological**
Very common Headache *Common* Neuropathy	*Rare* Neuropathy Headaches Paraesthesia
Gastrointestinal	**Gastrointestinal**
Very common Nausea *Common* Diarrhoea Discomfort and pain Vomiting	*Rare* Nausea and vomiting Abdominal discomfort and pain Diarrhoea
Hepatobiliary tract and pancreas	**Hepatobiliary tract and pancreas**
Common Abnormal liver function tests *Uncommon* Pancreatitis	*Uncommon* Pancreatitis *Rare* Abnormal pancreatic enzymes Abnormal liver function tests
Skin	**Skin**
Common Rashes	*Very rare* Rashes

Cases of pancreatitis have occurred rarely in adult patients and more commonly in children. However, it is not clear whether these cases were due to drug treatment or to their underlying HIV disease. Treatment with lamivudine should be stopped immediately if clinical signs or symptoms or laboratory abnormalities suggestive of pancreatitis occur.

In paediatric patients with a history of pancreatitis or other significant risk factors for the development of pancreatitis, the combination of lamivudine with other antiretroviral therapies should be used with extreme caution and only if there is no satisfactory alternative therapy.

Pancreatitis, which has been fatal in some cases has been observed in paediatric patients receiving lamivudine alone or in combination with other antiretroviral agents. In an open-label dose-escalation study, 14 patients (14%) developed pancreatitis while receiving monotherapy with lamivudine. Three of these patients died of complications of pancreatitis. In a second open-label study, 12 patients (18%) developed pancreatitis. In both these open label studies, the paediatric subjects had advanced, symptomatic HIV infection and many had received extensive prior therapy. In addition, many of the children had predisposing medical conditions or medications which could have contributed to pancreatitis. In study ACTG300 in therapy-naive subjects, pancreatitis was not observed in 236 patients randomised to lamivudine + zidovudine. Pancreatitis was observed in one patient in this study who received open-label lamivudine in combination with zidovudine and ritonavir following discontinuation of didanosine monotherapy. Paraesthesia and peripheral neuropathies were reported in 15 patients (15%) in one open study and 6 patients (9%) in the other open study and in 2 patients (1%) in ACTG300.

Table 6 lists all the adverse events, occurring at an incidence of 5% or more, reported in study EPV 20001.

Table 6 – Adverse Events (frequency ≥ 5%) in Study EPV 20001

BODY SYSTEM **Event**	**Lamivudine (OD)** **(N = 272)**		**Lamivudine (BD)** **(N = 273)**	
Subjects With Any Event	251	(92%)	263	(96%)
Nausea	103	(38%)	115	(42%)
Dizziness	78	(29%)	96	(35%)
Fatigue	78	(29%)	76	(28%)
Dreams	70	(26%)	63	(23%)
Rashes	62	(23%)	49	(18%)
Headaches	61	(22%)	49	(18%)
Diarrhoea	50	(18%)	48	(18%)
Sleep disorders	43	(16%)	44	(16%)
Viral respiratory infections	41	(15%)	37	(14%)
Vomiting	31	(11%)	41	(15%)
Ear, nose & throat infections	25	(9%)	37	(14%)
Anorexia	33	(12%)	22	(8%)
Mood disorders	30	(11%)	23	(8%)
Abdominal pain	22	(8%)	28	(10%)
Hypnagogic effects	19	(7%)	23	(8%)
Musculoskeletal pain	16	(6%)	24	(9%)
Fever	13	(5%)	26	(10%)
Dyspeptic symptoms	17	(6%)	19	(7%)
Fungal skin infections	18	(7%)	17	(6%)
Sinus disorders	14	(5%)	21	(8%)
Depressive disorders	12	(4%)	22	(8%)
Anxiety	15	(6%)	16	(6%)
Throat signs & symptoms	14	(5%)	16	(6%)
Cough	13	(5%)	16	(6%)
Pruritus	16	(6%)	12	(4%)
Sweating	11	(4%)	17	(6%)
Increased liver function tests	11	(4%)	13	(5%)
Decreased white cells	9	(3%)	14	(5%)
Taste disorders	9	(3%)	14	(5%)
Abdominal discomfort	8	(3%)	14	(5%)
Paraesthesia peripheral	13	(5%)	9	(3%)
Anaemia	4	(1%)	14	(5%)

Table 7 – Treatment emergent Grade 3 / 4 Laboratory Abnormalities (frequency ≥ 2%) in Study EPV 20001

Laboratory Parameter	OD N = 272 n (%)			BD N = 273 n (%)		
	Grade 3	Grade 4	Grade 3/4	Grade 3	Grade 4	Grade 3/4
Clinical Chemistry						
Increased ALT	5 (2)	3 (1)	8 (3)	6 (2)	5 (2)	11 (4)
Hypertriglyceridemia	8 (3)	2 (<1)	10 (4)	4 (1)	0	4 (1)
Increased AST	2 (<1)	2 (<1)	4 (1)	6 (2)	2 (<1)	8 (3)
Hyperamylasemia	7 (3)	0	7 (3)	2 (<1)	0	2 (<1)
Hematology Neutropenia	8 (3)	4 (1)	12 (4)	10 (4)	6 (2)	19 (6)

The data from the clinical trials have shown no significant difference in the frequency or severity of unwanted effects between administration of 150 mg twice daily and 300 mg once daily. There was however a higher incidence of hyperamylasaemia in the once daily regimen.

Adverse Events & laboratory findings in study ACTG300 are provided in **Tables 8 & 9.**

Table 8 – Selected Clinical Adverse Events and Physical Findings (≥5% Frequency) in Paediatric Patients in Study ACTG300

Adverse Event	Lamivudine plus Zidovudine (n = 236)	Didanosine (n = 236)
Body as a whole		
Fever	58 (25%)	75 (32%)
Digestive		
Hepatomegaly	25 (11%)	25 (11%)
Nausea & vomiting	18 (8%)	16 (7%)
Diarrhoea	18 (8%)	15 (6%)
Stomatitis	13 (6%)	28 (12%)
Splenomegaly	12 (5%)	18 (8%)
Respiratory		
Cough	36 (15%)	34 (18%)
Abnormal breathing sounds / wheezing	16 (7%)	21 (9%)
Ear, Nose and Throat		
Signs or symptoms of ears*	16 (7%)	13 (6%)
Nasal discharge or congestion	18 (8%)	25 (11%)
Other		
Skin rashes	24 (12%)	32 (14%)
Lymphadenopathy	22 (9%)	27 (11%)

*Includes pain, discharge, erythema, or swelling of an ear.

Selected laboratory abnormalities experienced by therapy-naive (≤ 56 days of antiretroviral therapy) paediatric patients are listed in **Table 9.**

Table 9 – Frequencies of Selected Laboratory Abnormalities in Paediatric Patients in Study ACTG300

Test (Abnormal Level)	Lamivudine plus Zidovudine	Didanosine
Neutropenia (ANC < 400/mm^3)	18 (8%)	8 (3%)
Anaemia (Hgb < 7.0 g/dL)	9 (4%)	5 (2%)
Thrombocytopenia (platelets < 50,000/mm^3)	3 (1%)	6 (3%)
ALT (> 10 x ULN)	3 (1%)	8 (3%)
AST (> 10 x ULN)	4 (2%)	9 (4%)
Lipase (> 2.5 x ULN)	6 (3%)	6 (3%)

Total Amylase (> 2.5 x ULN)	6 (3%)	6 (3%)

ULN = Upper limit of normal.
ANC = Absolute neutrophil count.

Post-Marketing Data

The following events have been reported during therapy for HIV disease with lamivudine alone and in combination with other anti-retroviral agents. With many it is unclear whether they are related to the medicinal products or are as a result of the underlying disease process.

The following convention has been utilised for the classification of undesirable effects:

Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1,000, <1/100), rare (>1/10,000, <1/1,000), very rare (<1/10,000).

Musculoskeletal and connective tissue disorders

Common: Arthralgia, muscle disorders

Rare: Rhabdomyolysis

Skin and subcutaneous tissue disorders

Common: Rash, alopecia

Blood and lymphatic systems disorders

Uncommon: Neutropenia, anaemia, thrombocytopenia

Very rare: Pure red cell aplasia

Nervous system disorders

Common: Headache

Very rare: Paraesthesia. Peripheral neuropathy has been reported although a causal relationship to treatment is uncertain.

Gastrointestinal disorders

Common: Nausea, vomiting, upper abdominal pain, diarrhoea

Rare: Pancreatitis, although a causal relationship to treatment is uncertain. Rises in serum amylase.

Hepatobiliary disorders

Uncommon: Transient rises in liver enzymes (AST, ALT)

Metabolism and nutrition disorders

Common: Hyperlactataemia

Rare: Lactic acidosis (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**)

General disorders and administrative site conditions

Common: Fatigue, malaise, fever

Paediatric population

The safety database to support lamivudine once daily dosing in paediatric patients comes from the ARROW Trial (COL105677) in which 669 HIV-1 infected paediatric subjects received abacavir and lamivudine either once or twice daily (see **Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials**). Primary safety assessment in the ARROW trial was based on Grade 3 and Grade 4 adverse events. The frequency of Grade 3 and 4 adverse events was similar among subjects randomized to once-daily dosing compared with subjects randomized to twice-daily dosing (see table below). One event of Grade 4 hepatitis in the once-daily cohort was considered as uncertain causality by the investigator and all other Grade 3 or 4 adverse events were considered not related by the investigator.

Table 10 – ARROW Study Randomization 3: Most Frequently Reported (2 or More Events Overall) of Grade 3 or 4 Adverse Events for Once- Versus Twice-Daily Dosing of Abacavir and Lamivudine by Dosing Frequency and Overall

	Twice-Daily ABC+ Lamivudine	**Once-Daily ABC+ Lamivudine**	**Total**
Total number of subjects	333	336	669
Total grade 3 or 4 AEs, n (%)	82 (25)	95 (28)	177 (26)
Hematological: computer, n (%)			
Leucopenia	2 (<1)	1 (<1)	3 (<1)
Neutropenia	15 (5)	23 (7)	38 (6)
Non-clinical anaemia	6 (2)	3 (<1)	9 (1)
Thrombocytopenia	6 (2)	10 (3)	16 (2)
Biochemical: computer, n (%)			
Hypoglycaemia	0	2 (<1)	2 (<1)
Raised ALT	5 (2)	1 (<1)	6 (<1)
Raised AST	3 (<1)	4 (1)	7 (1)
Raised bilirubin	2 (<1)	1 (<1)	3 (<1)
Raised liver	3 (<1)	5 (1)	8 (1)
Hematological: clinical report, n (%)			
Anaemia with clinical symptoms	5 (2)	7 (2)	12 (2)
Thrombocytopenia	0	2 (<1)	2 (<1)
Specific Infections, n (%)			
Measles	3 (<1)	1 (<1)	4 (<1)
Plasmodium falciparum malaria	16 (5)	16 (5)	32 (5)
Presumptive septicemia/ bacteremia	3 (<1)	3 (<1)	6 (<1)
Diarrhoeal disease, n (%)			
Acute diarrhoea, not investigated	2 (<1)	2 (<1)	4 (<1)
Lower respiratory tract, n (%)			
Pneumonia, no organism identified	2 (<1)	2 (<1)	4 (<1)
Eye, n (%)			
Cataract	0	2 (<1)	2 (<1)
Undiagnosed fevers, n (%)			
Acute febrile episode	0	2 (<1)	2 (<1)
Unknown, n (%)			
Dog bite	0	2 (<1)	2 (<1)

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. No specific signs or symptoms have been identified following acute overdose with lamivudine, apart from those listed as undesirable effects. Since lamivudine is dialysable, continuous haemodialysis could be used in the treatment of overdosage, although this has not been studied.

Treatment of overdosage should be symptomatic and consist of general supportive measures.

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 a potent, selective inhibitor of HIV-1 and HIV-2 replication *in vitro*. It is also active against zidovudine resistant clinical isolates of HIV.

In vitro, lamivudine demonstrates low cytotoxicity to peripheral blood lymphocytes, to established lymphocyte and monocyte-macrophage cell lines and to a variety of bone marrow progenitor cells. Lamivudine therefore has, *in vitro*, a high therapeutic index.

Lamivudine is metabolised intracellularly to the 5'-triphosphate which has an intracellular half-life of 10.5 - 15.5 hours. Lamivudine 5'-triphosphate is a weak inhibitor of the RNA and DNA dependent activities of HIV reverse transcriptase; its main mode of action is as a chain terminator of HIV reverse transcription.

Lamivudine does not interfere with cellular deoxynucleotide metabolism and has little effect on mammalian cell and mitochondrial DNA content.

The relationships between *in vitro* susceptibility of HIV to lamivudine and the clinical response to therapy remain under investigation. *In vitro* sensitivity testing has not been standardized and results may vary according to methodological factors.

Reduced *in vitro* sensitivity to lamivudine has been reported for HIV isolates from patients who have received lamivudine therapy.

No antagonistic effects *in vitro* were seen with lamivudine and other antiretrovirals (tested agents: abacavir, didanosine, nevirapine, zalcitabine, and zidovudine).

In vitro studies show that restored sensitivity to zidovudine may occur following serial passage of zidovudine-resistant HIV-1 in increasing concentrations of lamivudine. Furthermore, *in vivo*, there is evidence showing that lamivudine plus zidovudine delays the emergence of zidovudine-resistant isolates in individuals with no prior antiretroviral therapy.

Drug Resistance

Lamivudine-resistant isolates of HIV-1 have been selected *in vitro*. The resistant isolates showed reduced susceptibility to lamivudine and genotypic analysis showed that the resistance was due to specific substitution mutations in the HIV-1 reverse transcriptase at codon 184 from methionine to either isoleucine or valine. HIV-1 strains resistant to both lamivudine and zidovudine have been isolated.

Susceptibility of clinical isolates to lamivudine and zidovudine was monitored in controlled clinical trials. In patients receiving lamivudine monotherapy or combination therapy with lamivudine plus zidovudine, HIV-1

isolates from most patients became phenotypically and genotypically resistant to lamivudine within 12 weeks. In some patients harbouring zidovudine-resistant virus at baseline, phenotypic sensitivity to zidovudine was restored by 12 weeks of treatment with lamivudine and zidovudine. Combination therapy with lamivudine plus zidovudine delayed the emergence of mutations conferring resistance to zidovudine.

Cross-resistance

Cross-resistance among certain reverse transcriptase inhibitors has been observed. Cross- resistance between lamivudine and zidovudine has not been reported. In some patients treated with lamivudine alone or in combination with zidovudine, isolates have emerged with a mutation at codon 184, which confers resistance to lamivudine. In the presence of the 184 mutation, cross-resistance to didanosine and zalcitabine has been seen in some patients; the clinical significance is unknown. In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple reverse transcriptase inhibitors, including lamivudine, have emerged.

Clinical trial evidence from paediatric patients receiving lamivudine with other antiretroviral drugs (abacavir, nevirapine/efavirenz or zidovudine) has shown that the resistance profile observed in paediatric patients is similar to that observed in adults, in terms of the genotypic substitutions detected and their relative frequency.

Children receiving lamivudine oral solution concomitantly with other antiretroviral oral solutions in clinical trials developed viral resistance more frequently than children receiving tablets (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE), Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials** and **Section 5.2 PHARMACOKINETIC PROPERTIES).**

Clinical Trials

Clinical Endpoint Study

Clinical end-point data from a prospective study indicate that lamivudine in combination with zidovudine alone or in combination with zidovudine containing treatment regimens results in a significant reduction in the risk of disease progression and mortality.

NUCB3007 (CAESAR) was a multicentre, double-blind, placebo-controlled study comparing continued current therapy [zidovudine (AZT) alone (62% of patients) or zidovudine with didanosine (ddI) or zalcitabine (ddC) (38% of patients)] to the addition of lamivudine or lamivudine plus an investigational non-nucleoside reverse transcriptase inhibitor, randomised 1:2:1. A total of 1,840 HIV-infected adults with 25 to 250 (median, 126) CD4 cells/mm3 at baseline were enrolled: median age was 36 years, 87% were male, 83% were nucleoside- experienced, and 17% were therapy-naive. The median duration of treatment for each group was current therapy* 327 days, lamivudine plus current therapy* 360 days and lamivudine plus NNRTI** plus current therapy* 360 days. Results are summarised in **Table 11.**

Table 11 – Number of Patients (%) With At Least One HIV Disease Progression Event or Death – Intention to Treat Population

Endpoint	Current Therapy* (n = 471)	Lamivudine plus Current Therapy* (n = 907)	Lamivudine plus a NNRTI** plus Current Therapy* (n = 462)
HIV progression or death	95 (20%)	86 (9%)†	42 (9%)
Death	28 (6%)	23 (3%)‡	14 (3%)

*Current treatment = AZT (200 mg tds or 250 mg bd) monotherapy, AZT + ddI (250 mg bd) or AZT + ddC (0.75 mg tds).

**An investigational non-nucleoside reverse transcriptase inhibitor not approved in the Australia.

† p<0.0001 for Lamivudine + current therapy vs current therapy alone.

‡ p= 0.0007 for Lamivudine + current therapy vs current therapy alone.

The data showed there was a significant reduction in progression to the combined endpoint of a new AIDS event or death for patients who received lamivudine in combination with zidovudine containing regimens compared to patients maintained on zidovudine containing regimens alone (p<0.0001). The Hazard Ratio (HR) was 0.427 (95% confidence interval 0.318 - 0.572), or a 57% reduction in risk. In addition, the data indicated a significant reduction in death, regardless of causality, in the combination lamivudine plus zidovudine containing regimens as compared to the zidovudine containing regimens alone (p=0.0007); HR = 0.399 (95% CI 0.230-0.693) or a 60% reduction in risk.

ACTG320 was a randomised, double-blind, placebo-controlled study to compare indinavir, zidovudine (or stavudine) and lamivudine with the 2 drug regimen of zidovudine (or stavudine) and lamivudine in HIV-infected patients with CD4 counts ≤ 200 cells/mm3. Patients had received ≥ 3 months prior zidovudine therapy and had no prior exposure to protease inhibitors. A total of 1156 patients were randomised. The median duration of follow-up was 38 weeks. During the study there were 96 new AIDS-defining events or deaths, 63 (11%) in the zidovudine/lamivudine arm and 33 (6%) in the zidovudine/lamivudine/indinavir arm (estimated Hazard Ratio 0.50). There were 13 (6%) deaths in the zidovudine/lamivudine arm and 5 (2%) in the zidovudine/lamivudine/indinavir arm (Hazard Ratio 0.37). Both these results were statistically significant.

Surrogate Endpoint Studies in adults

Clinical efficacy in adults was based on the results of four pivotal studies in patients with or without prior antiretroviral therapy. Study designs are summarised in **Table 12.** All were randomised, double blind, multicentre studies. The characteristics of the patients at baseline are given in **Table 13.**

Table 12 – Summary of pivotal efficacy studies in adults

					Summary of results			
					0-24 weeks		**0-52 weeks**	
Study design – Pivotal studies in adults					**Mean time weighted change**		**52 week change from baseline**	
Report No (Protocol)	**Study Design Patients**	**Treatment doses**	**Number random-ised**	**Duration of treatment**	**CD4**	**Log_{10} HIV RNA**	**CD4**	**Log_{10} HIV RNA**
UCR/95/002 (NUCA3001)	DB, MC Zdv-naive CD4 200-500	Lam 300mg bd	87	24 weeks DB DB continuation	24	-0.59	-11	-0.32
		Zdv 200mg tds	93		17	-0.31	-53	-0.14
		Zdv + Lam 150mg	92		55	-1.12	61	-0.80
		Zdv + Lam 300mg	94		45	-1.15	60	-1.04
UCR/95/003 (NUCA3002)	DB, MC Zdv-experienced CD4 100-300	Zdv + ddC 0.75mg	86	24 weeks DB DB continuation	-2	-0.66	16	-0.50
		Zdv + Lam 150mg	84		38	-0.80	35	-0.48
		Zdv + Lam 300mg	84		39	-0.91	27	-0.55
GIO/94/003 (NUCB3001)	DB, MC Zdv-naive CD4 100-400	Zdv 200mg tds	64	24 weeks DB OL continuation	18	-0.57		
		Zdv + Lam 300mg	65		75	-1.33		
GIO/94/005 (NUCB3002)	DB, MC Zdv-experienced CD4 100-400	Zdv 200mg tds	73	24 weeks DB OL continuation	-18	-0.07		
		Zdv + Lam 150mg	75		38	-0.96		
		Zdv + Lam 300mg	75		32	-0.77		

Zidovudine given at a dose of 200 mg tds in all studies. Lamivudine dosed bd in all studies.

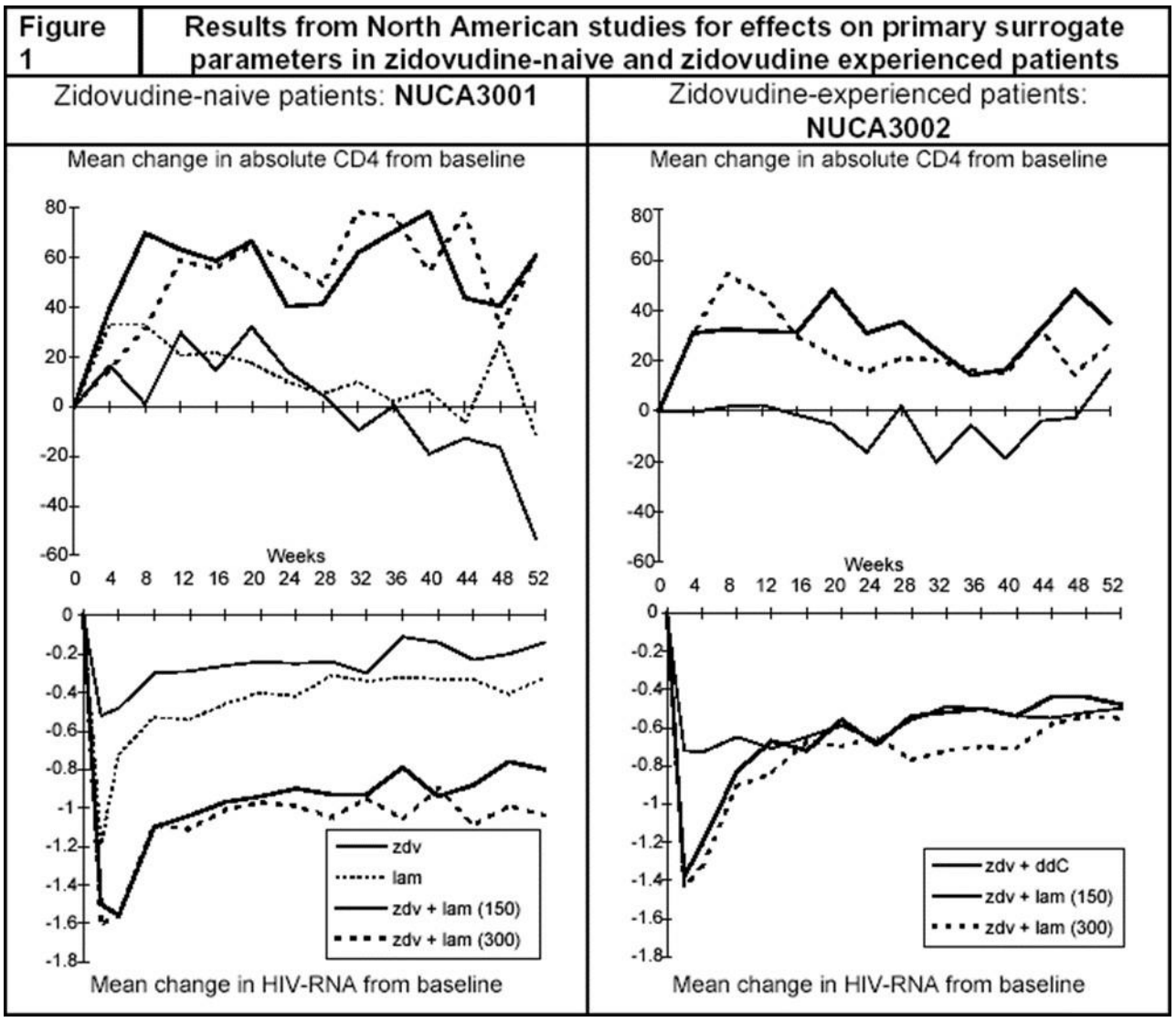
Table 13 – Characteristics of patients randomised to pivotal studies

	NUCA 3001	**NUCA3002**	**NUCB3001**	**NUCB3002**
Number of patients	366	254	129	223
Age (median) years	34	37	33	36
Asymptomatic HIV infection	80%	58%	64%	53%
Duration of prior antiretroviral therapy (months)	<1	24	<1	23
Baseline CD4 cells/mm^3 (median)	200 to 500 (352)	100 to 300 (211)	100 to 400 (260)	100 to 400 (241)

After 24 weeks: In zidovudine-naive patients the combination of lamivudine and zidovudine resulted in a highly significant ($p<0.001$) increase in absolute CD4 cell count and reduction in $\log_{10}$ HIV RNA relative to zidovudine monotherapy (600 mg/day) or lamivudine monotherapy (600 mg/day). Similarly, in zidovudine-experienced patients, the combination of lamivudine and zidovudine resulted in significantly greater improvements in CD4 cell count than either zidovudine monotherapy (600 mg/day) or a combination of zidovudine and zalcitabine (600 mg/day + 0.75 mg) and a significantly greater reduction in $\log_{10}$ HIV-RNA than zidovudine monotherapy.

In the North American studies (NUCA3001 and NUCA3002) patients were allowed to remain in the study with blinding intact until the last patient had completed the 24 week assessment. Analysis of the subset of patients receiving treatment for at least 52 weeks established that the clinical benefits on CD4 cell count and viral load were maintained compared to zidovudine monotherapy over this period ($p<0.001$). Results for CD4 count and $\log_{10}$ HIV-RNA are given in **Figure 1.**

Figure 1 **Results from North American studies for effects on primary surrogate parameters in zidovudine-naive and zidovudine experienced patients**



Adult Once Daily Dosing

EPV 20001 was a randomised, double-blind, controlled, multicentre study to evaluate the efficacy and safety of lamivudine 300 mg once daily vs. lamivudine 150 mg bid, as a component of triple therapy, in antiretroviral-naïve adults with HIV-1 infection.

The proportions of subjects with plasma HIV-1 RNA < 400 copies/mL for Intention-to-Treat Population using missing = failure analysis are summarised in the **Table 14:**

Table 14 – Summary of proportion of subjects with plasma HIV-1 RNA <400 copies/mL

Week	Lamivudine Dose Group		95% Confidence Interval
	OD N=278 % (n)	BID N=276 % (n)	
Week 4	53% (148)	52% (144)	(-7.7, 7.3)
Week 8	67% (187)	72% (199)	
Week 12	74% (207)	78% (216)	
Week 16	75% (208)	75% (207)	
Week 20	71% (196)	75% (207)	
Week 24	72% (199)	72% (198)	

The data demonstrate that the proportion of patients with plasma HIV-1 RNA <400 copies/mL at week 24 did not differ between treatment groups (od: 72%; bid: 72%). While the subjects in the od group had a baseline plasma HIV-1 RNA level 0.8 $\log_{10}$ copies/mL higher than those of the bid group (od: 5.1 $\log_{10}$ copies/mL; bid: 4.3 $\log_{10}$ copies/mL), the two groups were comparable with respect to on-treatment plasma HIV-1 RNA response. Twenty-nine (5%) of subjects had virological failure by week 24 but virus for resistance testing could only be isolated from 22 samples (11 subjects in each arm); the incidence of resistance was comparable in the treatment arms.

Median CD4+ cell count values and changes from baseline are summarised by treatment group in **Table 15.**

Table 15 – Median CD4+ cell and change from baseline (cells/mm3)

Week	Median CD4+ Count Median (range, n)		Median Change from baseline Median (range, n)	
	Lamivudine Dose Group		Lamivudine Dose Group	
	Lamivudine OD N=278	Lamivudine BID N=276	Lamivudine OD N=278	Lamivudine BID N=276
Baseline	340 (69-945, 278)	386 (90-1089, 276)	--	--
Week 12	432 (90-1357, 233)	477 (53-1383, 234)	95 (-300-605, 233)	85 (-475-721, 234)
Week 24	475 (123-1301, 209)	518 (105-1497, 212)	128 (-289-687, 209)	123 (-290-518, 212)

The data demonstrate that there were similar increases in median CD4+ cell counts observed between lamivudine treatment groups at week 24 (OD: 128 cells/mm^3; BID: 123 cells/mm^3).

The results for Study EPV 20001 are reported to 24 weeks; this study is currently ongoing.

EPV40001 was a small, randomised, open label, controlled multicentre study in Thailand to evaluate the efficacy and safety of lamivudine once daily (OAD) versus lamivudine BID and abacavir (ABC) once daily versus ABC BID as components of a combination regimen including zidovudine (ZDV), lamivudine and ABC in antiretroviral-naïve, HIV-1 infected adults. Subjects were randomised to receive ZDV/lamivudine (BID)/ABC (BID) (control group), ZDV/lamivudine (OAD)/ABC (BID) or ZDV/lamivudine (BID)/ABC (OAD).

The three groups showed comparable efficacy using AAUCMB (Average Area Under Curve Minus Baseline) for HIV-1 RNA at week 48, the primary efficacy parameter for establishing non-inferiority with a confidence interval of 0.4 $\log_{10}$ copies/mL (-2.0 $\log_{10}$ copies/mL control group, -2.0 $\log_{10}$ copies/mL lamivudine OAD group, -1.9 $\log_{10}$ copies/mL ABC OAD group) in the Intent to Treat Exposed population (ITTE).

Using a secondary parameter of efficacy, the proportions of subjects with plasma HIV-1 RNA < 400 copies/mL for the ITTE population in a missing = failure analysis are summarised in **Table 16**:

Table 16 – Summary of proportion of subjects with HIV-1 RNA <400 copies/mL

Week	Treatment group		
	Control Group (n = 50)	Lamivudine OAD (n = 50)	ABC OAD (n = 51)
4	62% (31)	62% (31)	59% (30)
12	84% (42)	76% (38)	76% (39)
24	84% (42)	70% (35)	71% (36)
48	78% (39)	66% (33)	63% (32)

Although there was a small numerical difference in treatment response in favour of the control group, this difference was primarily driven by a slightly higher incidence of treatment discontinuations in the OAD arms for reasons other than virological failure. Fifteen (10%) subjects had virological failure associated with resistance mutations; the incidence was comparable in the treatment arms.

There were similar increases in median CD4+ cell counts observed in the three treatment groups at week 48 (control group: +216 cells/mm^3; lamivudine OAD: +166 cells/mm^3; ABC OAD: +152 cells/mm^3).

Studies in children

Pharmacokinetic studies in children have established that relatively higher doses are required (8 mg/kg/day) to achieve comparable clinical exposure to that obtained with the recommended dose in adults (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION** and **Section 5.2 PHARMACOKINETIC PROPERTIES**).

An open label, dose-escalation study (lamivudine monotherapy) was conducted in children aged 3 months to 17 years who had received no or minimal antiretroviral therapy (Arm A) or had experienced toxicity or become refractory to prior antiretroviral therapy (Arm B). At one centre compassionate treatment of patients with recurrent opportunistic infections was also allowed (Arm C). Patients were dosed at 1, 2, 4, 8, 12 or 20 mg/kg/day in two divided doses for 24 weeks. Dose escalation/reduction to 8 mg/kg/day was allowed after 24 weeks of treatment.

Lamivudine showed evidence of antiviral activity in both naive (Arm A) and experienced (Arm B) patients but no consistent dose-response effects. The combined results for all dose levels in both groups are given in **Table 17**. No efficacy data are available on patients in Arm C.

Table 17 – Combined results for all dose levels in both groups

GROUP	**Arm A**		**Arm B**	
Patients	18		71	
Age (range)	3 months to 19 years		3 months to 19 years	
Age (median)	3.7 years		8.4 years	
CDC class P1	67%			
CDC class P2			97%	
RESULTS	Baseline	Change at Week 24[1]	Baseline	Change at Week 24[1]
CD4 count (/mm^3)	697	24	82	4
Log_{10} HIV-RNA (copies/mL)[2]	4.4	-0.2	4.9	-0.2

[1] Median changes from baseline through week 24

[2] Subset of patients with >1000 copies/mL at baseline

The peak increase in CD4 count was 104 cells/mm^3 at week 4 in Arm A and 6 cells/mm^3 in Arm B. CD4 counts were maintained at or close to baseline values in both arms of the study to week 48. Serum HIV-1- RNA concentrations decreased during the same period and for the subset of patients with >1000 copies/mL at

baseline was significantly different to baseline in Arm A at week 48 (-0.7 log_{10}, p=0.031), and in Arm B at week 12 (-0.2 log_{10}, p=0.009), week 24 (-0.2 log_{10}, p=0.008) and week 48 (0.2 log_{10}, p=0.032).

ACTG300 was a multicentre randomized double-blind study, in paediatric patients, that provided for comparison of lamivudine plus zidovudine to didanosine monotherapy. The median duration on study medication was 10.1 months for patients receiving lamivudine + zidovudine and 9.2 months for children receiving didanosine monotherapy. **Table 18** provides details of the changes from baseline for the two treatment groups and **Table 19** the number of patients reaching primary clinical endpoint (disease progression or death):

Table 18 – Results from Study ACTCG300

	ZDV/LAM		**ddl**	
Patients	236		236	
Age in years (median)	2.7		2.8	
CDC Category **N: no signs/symptoms**	35 (15%)		34 (14%)	
A: mild signs/symptoms	116 (49%)		105 (44%)	
B: moderate signs/symptoms	50 (21%)		65 (28%)	
C: Severe signs/symptoms	35 (15%)		32 (14%)	
Results	Baseline	Change from baseline [1]	Baseline	Change from baseline [1]
Median HIV-1 RNA (log_{10} copies/mL)	5.1	-0.6 [2]	5.1	-0.4 [2]
CD4 (cells/mL)	703.0	94.0 [2]	658.5	0.0 [2]

1: Median changes from baseline through to week 36.
2: Statistically significant difference

Table 19 – Number of Patients (%) Reaching a Primary Clinical Endpoint (Disease Progression or Death)

Endpoint	**Lamivudine plus Zidovudine (n = 236)**	**Didanosine (n = 236)**
HIV disease progression or death (total)	15 (6.4%)	39 (17%)
Physical growth failure	7 (3.0%)	7 (3%)
Central nervous system deterioration	4 (1.7%)	12 (5.1%)
CDC Clinical Category C	2 (0.8%)	8 (3.4%)
Death	2 (1%)	12 (5%)

This study demonstrated a significant benefit of combination zidovudine/lamivudine therapy over didanosine monotherapy by clinical and laboratory measures.

Paediatric Once Daily Dosing

A randomised comparison of a regimen including once daily vs twice daily dosing of abacavir and lamivudine was undertaken within a randomised, multicentre, controlled study of HIV infected, paediatric patients, conducted in Uganda and Zimbabwe. 1206 paediatric patients aged 3 months to 17 years enrolled in the ARROW Trial (COL105677) and were dosed according to the weight - band dosing recommendations in the World Health Organisation treatment guidelines (Antiretroviral therapy of HIV infection in infants and children, 2006). Subjects were ART naïve before enrolment and initiated treatment with an NNRTI + ABC (twice daily) + lamivudine (twice daily) with or without ZDV. After 36 weeks on antirevtroviral therapy which included twice daily abacavir and lamivudine, 669 eligible children who had been on ART for at least 36 weeks, were currently taking lamivudine+abacavir twice daily as part of their ART regimen and expected to stay on these two drugs for at least the next 12 weeks were randomised to either continue twice daily dosing

or switch to once daily abacavir and lamivudine for at least 96 weeks. At the time of the once daily versus twice daily randomisation, median age was 5.5 years (range 1.8 – 16.9 years). Most subjects (58.9%) were WHO Stage 3 and most subjects (68.5%) had CD4 at ≥ 30%. The results are summarised in the **Table 20** below.

Table 20 – Virological Response Based on Plasma HIV-1 RNA less than 80 copies/ml at Week 48 and Week 96 in the Once Daily versus Twice Daily abacavir + lamivudine randomisation of ARROW (Observed Analysis)

	Twice Daily N (%)	**Once Daily N (%)**
Week 0 (After ≥36 Weeks on Treatment)		
Plasma HIV-1 RNA <80 c/mL	250/331 (76)	237/335 (71)
Risk difference (once daily-twice daily)	-4.8% (95% CI -11.5% to +1.9%), p=0.16	
Week 48		
Plasma HIV-1 RNA <80 c/mL	242/331 (73)	236/330 (72)
Risk difference (once daily-twice daily)	-1.6% (95% CI -8.4% to +5.2%), p=0.65	
Week 96		
Plasma HIV-1 RNA <80 c/mL	234/326 (72)	230/331 (69)
Risk difference (once daily-twice daily)	-2.3% (95% CI -9.3% to +4.7%), p=0.52	

The abacavir/lamivudine once daily dosing group was demonstrated to be non-inferior to the twice daily group according to the pre-specified non-inferiority margin of -12%, for the primary endpoint of < 80 copies/mL at Week 48 as well as at Week 96 (secondary endpoint) and all other thresholds tested (< 200 copies/mL, <400 copies/mL, < 1000 copies/mL), which all fell well within this non-inferiority margin. Subgroup analyses testing for heterogeneity of once vs twice daily demonstrated no significant effect of sex, age, or viral load at randomisation. Conclusions supported non-inferiority regardless of analysis method.

Note that the endpoint of viral load < 50 copies/mL could not be assessed due to low volumes of stored plasma samples from small children.

At the time of randomisation to once daily vs twice daily dosing (Week 0), those patients who had received tablet formulations had a higher rate of viral load suppression than those who had received any solution formulations at any time. These differences were observed in each different age group studied. This difference in suppression rates between tablets and solutions remained through Week 96 with once daily dosing.

Table 21 – Proportions of Subjects in the Once Daily versus Twice Daily Abacavir+Lamivudine Randomisation of ARROW with Plasma HIV-1 RNA <80 copies/mL: Subgroup Analysis by Formulation

	Twice Daily Plasma HIV-1 RNA <80 c/mL: n/N (%)	Once Daily Plasma HIV-1 RNA <80 c/mL: n/N (%)
Week 0 (after 36 weeks on Treatment)		
Any solution regimen at any time	14/26 (54)	15/30 (50)
All tablet based regimen throughout	236/305 (77)	222/305 (73)
Week 96		
Any solution regimen at any time	13/26 (50)	17/30 (57)
All tablet based regimen throughout	221/300 (74)	213/301 (71)

Genotypic resistance analyses were conducted on samples with plasma HIV-1 RNA > 1000 copies/ml. More cases of resistance were detected among patients who had received lamivudine solution, in combination with

other antiretroviral solutions, compared with those who received similar doses of tablet formulation. This is consistent with the lower rates of antiviral suppression observed in these patients (see **Section 5.2 PHARMACOKINETIC PROPERTIES - Pharmacokinetics in children**).

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. approximately 4 mg/kg/day (as 150 mg twice daily) C_{max} is in the order of 1-1.9 µg/mL.

When a capsule formulation of lamivudine was ingested with food, there was a significant reduction in C_{max} (47%) and extension to T_{max} (2.2 hours). Although absorption of lamivudine was delayed, the amount of drug absorbed is not reduced.

The 150 mg tablet is bioequivalent and dose proportional to the 300 mg tablet with respect to AUC_{∞}, C_{max} and T_{max}.

The active moiety, intracellular lamivudine triphosphate, has a prolonged terminal half-life in the cell (10.5 to 15.5 hours) compared to the plasma lamivudine half-life (5 to 7 hours). In 60 healthy adult volunteers, lamivudine 300 mg tablets once daily has been demonstrated to be pharmacokinetically equivalent at steady-state to lamivudine 150 mg tablets twice daily with respect to intracellular triphosphate AUC_{24} and C_{max}.

The mean intracellular lamivudine triphosphate $C_{0,ss}$ was reduced by 16% and the mean $C_{24,ss}$ was reduced by 19% in volunteers given lamivudine 300mg once daily compared with lamivudine 150mg twice daily. The clinical relevance of the lower C_{min} is unknown.

A study compared the pharmacokinetics of lamivudine tablets 300 mg once daily and lamivudine tablets 150 mg twice daily in 60 healthy, fasted volunteers. Steady state plasma lamivudine AUCs were comparable for the two dosage regimens (mean ratio 0.94, 90% CI: 0.92 - 0.97) whereas the C_{max} was increased by 66% (mean ratio 90% CI: 1.57 - 1.74) and C_{trough} was 53% lower (mean ratio 90% CI: 0.44 - 0.50) with the 300mg once daily. The clinical significance of the lower trough levels in unknown.

A bioequivalence study was conducted comparing the generic Lamivudine 300mg 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-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 the physiochemical and pharmacokinetic data, assuming that the patient crushes and transfers 100% of the tablet and ingests immediately.

Absorption differences have been observed between adult and paediatric populations (see **Section 5.2 PHARMACOKINETIC PROPERTIES – Pharmacokinetics in Children**).

Distribution

From intravenous studies, the mean volume of distribution is 1.3 L/kg and the mean terminal half-life of elimination is 5 to 7 hours.

Limited data show lamivudine penetrates the central nervous system and reaches the cerebrospinal fluid. The mean ratio CSF/serum lamivudine concentration 2-4 hours after oral administration was approximately 0.12. The true extent of penetration or relationship with any clinical efficacy is unknown.

Metabolism

Co-administration of zidovudine and lamivudine in a study of twelve asymptomatic patients with HIV caused minimal changes in lamivudine levels. The availability (mean AUC) of zidovudine was increased by 13%, mean C_{max} was increased by 28%, and mean $t_{½}$ reduced by 11%. There was considerable individual variation and the changes were not statistically significant. The relevance of these changes to clinical efficacy and safety is not known.

The likelihood of adverse drug interactions with lamivudine is low due to limited metabolism and plasma protein binding and almost complete renal elimination of unchanged drug. An interaction with trimethoprim, a constituent of trimethoprim with sulphamethoxazole causes a 40% increase in lamivudine exposure at therapeutic doses.

Excretion

The mean systemic clearance of lamivudine is approximately 0.32 L/kg/h, with predominantly renal clearance (>70%) via active tubular secretion, but little (<10%) hepatic metabolism.

A single dose pharmacokinetic study (n=16) in HIV-infected patients with normal renal function and with moderate (Cl_{cr} <30 mL/min and >10 mL/min) or end stage renal impairment (Cl_{cr} <10 mL/min) showed there was a linear relationship between lamivudine clearance and renal function. A dosage adjustment is required in patients with creatinine clearance below 50 mL/min (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION**).

A single dose pharmacokinetic study (n = 24) in patients with moderate and severe hepatic impairment in comparison with healthy subjects showed no statistically significant differences for any of the mean pharmacokinetic parameters assessed. There was a trend towards reduced renal clearance in severely impaired subjects to an average of 76% (90% CI: 58% to 101%) relative to healthy control subjects.

Pharmacokinetics in children

The absolute bioavailability of lamivudine (approximately 58-66%) was lower and more variable in paediatric patients below 12 years of age. In children, administration of tablets given concomitantly with other antiretroviral tablets delivered higher plasma lamivudine AUC $_{\infty}$ and C_{max} than oral solution given concomitantly with other antiretroviral oral solutions. Children receiving lamivudine oral solution according to the recommended dosage regimen achieve plasma lamivudine exposure within the range of values observed in adults. Children receiving lamivudine oral tablets according to the recommended dosage regimen achieve higher plasma lamivudine exposure than children receiving oral solution because higher mg/kg doses are administered with the tablet formulation and the tablet formulation has higher bioavailability (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION**). Paediatric pharmacokinetic studies with both oral solution and tablet formulations have demonstrated that once daily dosing provides equivalent AUC_{0-24} to twice daily dosing of the same total daily dose. However, C_{max} is approximately 2-fold higher with once daily dosing compared to twice daily dosing.

Table 22 – Pharmacokinetic Parameters [Geometric Mean (95% CI)] after Repeat Dosing of Lamivudine in 3 Paediatric Trials

	Trial (Number of Subjects)					
	ARROW PK (n = 35)		PENTA-13 (n = 19)		PENTA-15 (n = 17)[a]	
Age Range	3-12 years		2-12 years		3-36 months	
Formulation	Tablet		Solution and Tablet[b]		Solution	
Parameter	Once Daily	Twice Daily	Once Daily	Twice Daily	Once Daily	Twice Daily
C_{max} (mcg/mL)	3.17 (2.76, 3.64)	1.80 (1.59, 2.04)	2.09 (1.80, 2.42)	1.11 (0.96, 1.29)	1.87 (1.65, 2.13)	1.05 (0.88, 1.26)
$AUC_{(0-24)}$ (mcg•h/mL)	13.0 (11.4, 14.9)	12.0 (10.7, 13.4)	9.80 (8.64, 11.1)	8.88 (7.67, 10.3)	8.66 (7.46, 10.1)	9.48 (7.89, 11.4)

[a] N = 16 for PENTA-15 C_{max}

[b] Five subjects in PENTA-13 received lamivudine tablets

Plasma lamivudine concentrations following oral solution administration were obtained in a subset of children who were enrolled in the full ARROW study. The ARROW PK Substudy 2 was designed to compare the plasma pharmacokinetics of lamivudine when co-administered as oral solution versus scored tablet (n=19) of HIV-1 infected children (weighing 12 to 15 kg and aged 2 to 4 years) who were enrolled in the full ARROW study. The children were receiving lamivudine oral solution (twice daily) and were ready to switch to tablet form (twice daily). For lamivudine, the oral solution dose was 60 mg twice daily and the tablet dose was 75 mg twice daily (½ of a scored lamivudine-zidovudine tablet). Serial pharmacokinetic samples were obtained after at least 24 weeks on solution formulation and again at 4 weeks after switching to the tablet formulation. The plasma exposures of lamivudine were higher following the administration of lamivudine as the lamivudine- zidovudine tablet with dose normalised C_{max} and $AUC_{(0-\tau)}$ values approximately 55% and 58% higher, respectively, compared to the lamivudine oral solution.

There are limited pharmacokinetic data for patients less than three months of age. In neonates one week of age, lamivudine oral clearance was reduced when compared to paediatric patients and is likely to be due to immature renal function and variable absorption. Therefore, to achieve similar adult and paediatric exposure, for neonates a dose of 2 mg/Kg should be considered. Glomerular filtration estimates suggests that to achieve similar adult and paediatric exposure, the recommended dose for children aged six weeks and older could be 4mg/kg twice a day. However there is no data available in neonates older than one week old.

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 lamivudine did not cause chromosomal damage in bone marrow cells *in vivo* or cause DNA damage in primary hepatocytes at estimated exposures many times higher than those observed clinically.

Lamivudine should not represent a genotoxic hazard to patients undergoing treatment.

Carcinogenicity

When lamivudine was administered orally to separate groups of rodents at doses up to 2000 times (mice and male rats) and 3000 (female rats) mg/kg/day, there was no evidence of a carcinogenic effect due to lamivudine in the mouse study. In the rat study there was an increased incidence of endometrial tumours at the highest dose (approximately 70 times the estimated human exposure at the recommended therapeutic dose of one tablet twice daily, based on AUC). However, the relationship of this increase to treatment is uncertain.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The tablets also contain the following excipients: microcrystalline cellulose, sodium starch glycollate Type A, magnesium stearate and the film coating contains propylene glycol with Opadry Complete Film Coating System 03H58736 White (Proprietary Ingredient Number: 106640).

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 30ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

LAMIVUDINE ALPHAPHARM 150 mg film-coated tablets

Container type: PVC/PVDC/Al blister packs* or HDPE bottles.

Pack size: 60 film-coated tablets

LAMIVUDINE ALPHAPHARM 300 mg film-coated tablets

Container type: PVC/PVDC/Al blister packs* or HDPE bottles

Pack size: 30 film-coated tablets

* Not marketed in Australia.

Australian Register of Therapeutic Goods (ARTG)

AUST R 167591 – LAMIVUDINE ALPHAPHARM lamivudine 150 mg film-coated tablet bottle

AUST R 167592 – LAMIVUDINE ALPHAPHARM lamivudine 150 mg film-coated tablet blister pack

AUST R 167594 – LAMIVUDINE ALPHAPHARM lamivudine 300 mg film-coated tablet bottle

AUST R 167593 – LAMIVUDINE ALPHAPHARM lamivudine 300 mg film-coated tablet blister pack

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.

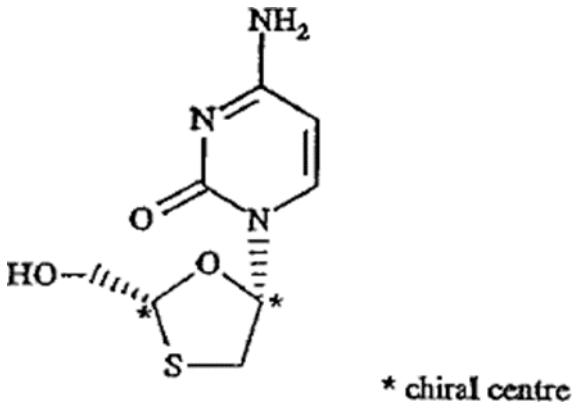
6.7 PHYSICOCHEMICAL PROPERTIES

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

Chemical Structure

Chemical name: (2R-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

CAS Number

134678-17-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Limited

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Millers Point NSW 2000

www.mylan.com.au

9 DATE OF FIRST APPROVAL

16/02/2012

10 DATE OF REVISION

04/02/2022

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes
4.4	Update to transmission of infection
4.9	Update to overdose information
6.5	Addition of AUST R numbers

Lamivudine Alphapharm_pi\Feb22/00