

## Lamivudine Tablets and Oral Solution

### LAMIVIR

**WARNING: RISK OF LACTIC ACIDOSIS, EXACERBATIONS OF HEPATITIS B IN CO-INFECTED PATIENTS UPON DISCONTINUATION OF LAMIVIR, DIFFERENT FORMULATIONS OF LAMIVIR.**

**LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING LAMIVUDINE AND OTHER ANTIRETROVIRALS (SEE WARNINGS AND PRECAUTIONS). SUSPEND TREATMENT IF CLINICAL OR LABORATORY FINDINGS SUGGESTIVE OF LACTIC ACIDOSIS OR PRONOUNCED HEPATOTOXICITY OCCUR (SEE WARNINGS AND PRECAUTIONS).**

**SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO ARE CO-INFECTED WITH HEPATITIS B VIRUS (HBV) AND HUMAN IMMUNODEFICIENCY VIRUS (HIV-1) AND HAVE DISCONTINUED LAMIVUDINE. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE LAMIVUDINE AND ARE CO-INFECTED WITH HIV-1 AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS AND PRECAUTIONS).**

**LAMIVIR TABLETS AND ORAL SOLUTION (USED TO TREAT HIV INFECTION) CONTAIN A HIGHER DOSE OF THE ACTIVE INGREDIENT (LAMIVUDINE) THAN LAMIVUDINE- HBV TABLETS AND ORAL SOLUTION (USED TO TREAT CHRONIC HBV INFECTION). PATIENTS WITH HIV-1 INFECTION SHOULD RECEIVE ONLY DOSING FORMS APPROPRIATE FOR THE TREATMENT OF HIV (SEE WARNINGS AND PRECAUTIONS).**

### COMPOSITION

#### **LAMIVIR-150 Tablets**

Each film-coated tablet contains:

Lamivudine ..... 150 mg

#### **LAMIVIR Oral Solution**

Each 5 ml contains:

Lamivudine ..... 50 mg

## DOSAGE FORM

Tablets and Oral solution

## PHARMACOLOGY

### Pharmacodynamics

Intracellularly, lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is the inhibition of reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue into viral DNA. 3TC-TP is a weak inhibitor of mammalian DNA polymerases  $\alpha$ ,  $\beta$  and  $\gamma$ .

### Pharmacokinetics

The pharmacokinetic properties of lamivudine have been studied in asymptomatic, HIV-1 infected-adult patients after administration of single intravenous (I.V.) doses ranging from 0.25 to 8 mg/kg, as well as single and multiple (twice-daily regimen) oral doses ranging from 0.25 to 10 mg/kg.

The pharmacokinetic properties of lamivudine have also been studied as single and multiple oral doses ranging from 5mg to 600 mg/day, administered to HBV - infected patients. The steady-state pharmacokinetic properties of the lamivudine 300 mg tablet once daily for 7 days compared with the lamivudine 150-mg tablet twice daily for 7 days were assessed in a crossover study in 60 healthy volunteers. Lamivudine 300 mg once daily resulted in lamivudine exposures that were similar to lamivudine 150 mg twice daily with respect to plasma  $AUC_{24,ss}$ ; however,  $C_{max,ss}$  was 66% higher and the trough value was 53% lower compared with the 150 mg twice-daily regimen. Intracellular lamivudine triphosphate exposures in peripheral blood mononuclear cells were also similar with respect to  $AUC_{24,ss}$  and  $C_{max24,ss}$ ; however, trough values were lower compared with the 150 mg twice-daily regimen. Inter-subject variability was greater for intracellular lamivudine triphosphate concentrations versus lamivudine plasma trough concentrations. The clinical significance of observed differences for both plasma lamivudine concentrations and intracellular lamivudine triphosphate concentrations is not known.

**Absorption and Bioavailability:** Lamivudine was rapidly absorbed after oral administration in HIV-1 infected patients. Absolute bioavailability in 12 adult patients was  $86\% \pm 16\%$  (mean  $\pm$  SD) for the 150-mg tablet and  $87\% \pm 13\%$  for the oral solution. After oral administration of 2 mg/kg twice a day to 9 adults with HIV-1, the peak serum lamivudine concentration ( $C_{max}$ ) was  $1.5 \pm 0.5$  mcg/mL (mean  $\pm$  SD). The area under the plasma concentration versus time curve (AUC) and  $C_{max}$  increased in proportion to the oral dose over the range from 0.25 to 10 mg/kg.

The accumulation ratio of lamivudine in HIV-1-positive asymptomatic adults with normal renal function was 1.50 following 15 days of oral administration of 2 mg/kg twice daily.

### Effects of Food on Oral Absorption

An investigational 25-mg dosage form of lamivudine was administered orally to 12 asymptomatic, HIV-1-infected patients on 2 occasions, once in the fasted state and once with food (1099 kcal; 75 grams fat, 34 grams protein, 72 grams carbohydrate). Absorption of lamivudine was slower in the fed state ( $T_{\max}$ :  $3.2 \pm 1.3$  hours) compared with the fasted state ( $T_{\max}$ :  $0.9 \pm 0.3$  hours);  $C_{\max}$  in the fed state was  $40\% \pm 23\%$  (mean  $\pm$  SD) lower than in the fasted state. There was no significant difference in systemic exposure ( $AUC_{\infty}$ ) in the fed and fasted states; therefore, lamivudine tablets and oral solution may be administered with or without food.

**Distribution:** The apparent volume of distribution after I.V. administration of lamivudine to 20 patients was  $1.3 \pm 0.4$  L/kg, suggesting that lamivudine distributes into extravascular spaces. Volume of distribution was independent of dose and did not correlate with body weight.

Binding of lamivudine to human plasma proteins is low (<36%). *In vitro* studies showed that over the concentration range of 0.1 to 100 mcg/mL, the amount of lamivudine associated with erythrocytes ranged from 53% to 57% and was independent of concentration.

**Metabolism:** Metabolism of lamivudine is a minor route of elimination. In man, the only known metabolite of lamivudine is the trans-sulfoxide metabolite. Within 12 hours after a single oral dose of lamivudine in 6 HIV-1-infected adults,  $5.2\% \pm 1.4\%$  (mean  $\pm$  SD) of the dose was excreted as the trans-sulfoxide metabolite in the urine. Serum concentrations of this metabolite have not been determined.

**Elimination:** The majority of lamivudine is eliminated unchanged in urine by active organic cationic secretion. In 9 healthy subjects given a single 300 mg oral dose of lamivudine, renal clearance was  $199.7 \pm 56.9$  mL/min (mean  $\pm$  SD). In 20 HIV-1-infected patients given a single IV dose, renal clearance was  $280.4 \pm 75.2$  mL/min (mean  $\pm$  SD), representing  $71\% \pm 16\%$  (mean  $\pm$  SD) of total clearance of lamivudine. In most single-dose studies in HIV-1-infected patients, HBV-infected patients, or healthy subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life ( $t_{1/2}$ ) ranged from 5 to 7 hours. In HIV-1-infected patients, total clearance was  $398.5 \pm 69.1$  mL/min (mean  $\pm$  SD). Oral clearance and elimination half-life were independent of dose and body weight over an oral dosing range of 0.25 to 10 mg/kg.

### **Special Populations**

**Renal Impairment:** The pharmacokinetic properties of lamivudine have been determined in a small group of HIV-1-infected adults with impaired renal function (Table 1).

**Table 1: Pharmacokinetic Parameters (Mean  $\pm$  SD) After a Single 300 mg Oral Dose of Lamivudine in 3 Groups of Adults with Varying Degrees of Renal Function**

Parameter	Creatinine Clearance Criterion (Number of Subjects)		
	>60 mL/min (n = 6)	10-30 mL/min (n = 4)	<10 mL/min (n = 6)
Creatinine clearance (mL/min)	111 $\pm$ 14	28 $\pm$ 8	6 $\pm$ 2
C <sub>max</sub> (mcg/mL)	2.6 $\pm$ 0.5	3.6 $\pm$ 0.8	5.8 $\pm$ 1.2
AUC <sub>∞</sub> (mcg·hr/mL)	11.0 $\pm$ 1.7	48.0 $\pm$ 19	157 $\pm$ 74
Cl/F (mL/min)	464 $\pm$ 76	114 $\pm$ 34	36 $\pm$ 11

Exposure (AUC<sub>∞</sub>), C<sub>max</sub>, and half-life increased with diminishing renal function (as expressed by creatinine clearance). Apparent total oral clearance (Cl/F) of lamivudine decreased as creatinine clearance decreased. T<sub>max</sub> was not significantly affected by renal function. Based on these observations, it is recommended that the dosage of lamivudine be modified in patients with renal impairment (see **DOSAGE AND ADMINISTRATION**).

Based on a study in otherwise healthy subjects with impaired renal function, hemodialysis increased lamivudine clearance from a mean of 64 to 88 mL/min; however, the length of time of hemodialysis (4 hours) was insufficient to significantly alter mean lamivudine exposure after a single-dose administration. Continuous ambulatory peritoneal dialysis and automated peritoneal dialysis have negligible effects on lamivudine clearance. Therefore, it is recommended, following correction of dose for creatinine clearance, that no additional dose modification should be made after routine hemodialysis or peritoneal dialysis. It is not known whether lamivudine can be removed by continuous (24-hour) hemodialysis.

The effects of renal impairment on lamivudine pharmacokinetics in pediatric patients are not known.

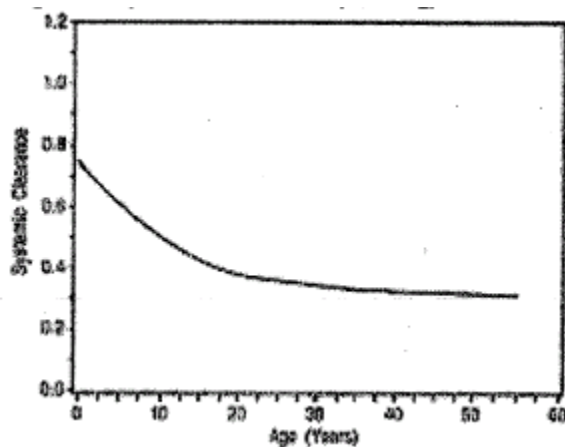
**Hepatic Impairment:** The pharmacokinetic properties of lamivudine have been determined in adults with impaired hepatic function. Pharmacokinetic parameters were not altered by diminishing hepatic function; therefore, no dose adjustment for lamivudine is required for patients with impaired hepatic function. Safety and efficacy of lamivudine have not been established in the presence of decompensated liver disease.

**Pediatric Patients:** In Study NUCA2002, the pharmacokinetic properties of lamivudine were assessed in a subset of 57 HIV-1-infected pediatric patients (age range: 4.8 months to 16 years, weight range: 5 to 66 kg) after oral and I.V.

administration of 1, 2, 4, 8, 12, and 20 mg/kg/day. In the 9 infants and children (range: 5 months to 12 years of age) receiving oral solution 4 mg/kg twice daily (the usual recommended pediatric dose), absolute bioavailability was  $66\% \pm 26\%$  (mean  $\pm$  SD), which was less than the  $86\% \pm 16\%$  (mean  $\pm$  SD) observed in adults. The mechanism for the diminished absolute bioavailability of lamivudine in infants and children is unknown.

Systemic clearance decreased with increasing age in pediatric patients, as shown in Figure 1.

**Figure 1: Systemic Clearance (L/hr.kg) of Lamivudine in Relation to Age**



After oral administration of lamivudine 4 mg/kg twice daily to 11 pediatric patients ranging from 4 months to 14 years of age,  $C_{max}$  was  $1.1 \pm 0.6$  mcg/mL and the half-life was  $2.0 \pm 0.6$  hours. (In adults with similar blood sampling, the half-life was  $3.7 \pm 1$  hour.) Total exposure to lamivudine, as reflected by mean AUC values, was comparable between pediatric patients receiving an 8 mg/kg/day dose and adults receiving a 4 mg/kg/day dose. Distribution of lamivudine into cerebrospinal fluid (CSF) was assessed in 38 pediatric patients after multiple oral dosing with lamivudine. CSF samples were collected between 2 and 4 hours post-dose. At the dose of 8 mg/kg/day, CSF lamivudine concentrations in 8 patients ranged from 5.6% to 30.9% (mean  $\pm$  SD of  $14.2\% \pm 7.9\%$ ) of the concentration in a simultaneous serum sample, with CSF lamivudine concentrations ranging from 0.04 to 0.3 mcg/mL.

Limited, uncontrolled pharmacokinetic and safety data are available from administration of lamivudine (and zidovudine) to 36 infants, up to 1 week of age, in 2 studies in South Africa. In these studies, lamivudine clearance was substantially reduced in 1-week-old neonates relative to pediatric patients (>3 months of age) studied previously. There is insufficient information to establish the time course of changes in clearance between the immediate neonatal period and the age ranges of >3 months old.

**Geriatric Patients:** The pharmacokinetics of lamivudine after administration of lamivudine to patients over 65 years of age have not been studied.

**Gender:** There are no significant gender differences in lamivudine pharmacokinetics.

**Race:** There are no significant racial differences in lamivudine pharmacokinetics.

## INDICATIONS

**LAMIVIR** is a nucleoside analogue indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (hiv-1) infection.

## DOSAGE AND ADMINISTRATION

### Adults and Adolescents (>16 years of age)

The recommended oral dose of **LAMIVIR** in HIV-1 infected adults and adolescents >16 years of age is 300 mg daily, administered as either 150 mg twice daily or 300 mg once daily, in combination with other antiretroviral agents.

If lamivudine is administered to a patient infected with HIV-1 and HBV, the dosage indicated for HIV-1 therapy should be used as part of an appropriate combination regimen (see **WARNINGS AND PRECAUTIONS**).

### Pediatric Patients

The recommended oral dose of **LAMIVIR** Oral Solution in HIV-1 infected pediatric patients, 3 months to 16 years of age, is 4 mg/kg twice daily (up to a maximum of 150 mg twice a day), administered in combination with other antiretroviral agents.

**LAMIVIR** is also available as a scored tablet for HIV-1 infected pediatric patients who weigh  $\geq 14$  kg for whom a solid dosage form is appropriate. Before prescribing lamivudine tablets, children should be assessed for the ability to swallow tablets. If a child is unable to reliably swallow lamivudine tablets, the oral solution formulation should be prescribed. The recommended oral dosage of lamivudine tablets for HIV-1-infected pediatric patients is presented in Table 2.

**Table 2: Dosing Recommendations for Lamivudine Tablets in Pediatric Patients**

Weight (kg)	Dosage Regimen Using Scored 150 mg Tablet		Total Daily Dose
	AM Dose	PM Dose	
14 to 21	½ tablet (75 mg)	½ tablet (75 mg)	150 mg
>21 to <30	½ tablet (75 mg) <sup>3</sup>	1 tablet (150 mg)	225 mg
$\geq 30$	1 tablet (150 mg)	1 tablet (150 mg)	300 mg

### Patients with Renal Impairment

Dosing of lamivudine is adjusted in accordance with renal function. Dosage adjustments are listed in Table 3 (see **PHARMACOLOGY**).

**Table 3: Adjustment of Dosage of Lamivudine in Adults and Adolescents (>30 kg) in Accordance with Creatinine Clearance**

<b>Creatinine Clearance (mL/min)</b>	<b>Recommended Dosage of Lamivudine</b>
≥50	150 mg twice daily or 300 mg once daily
30–49	150 mg once daily
15–29	150 mg first dose, then 100 mg once daily
5–14	150 mg first dose, then 50 mg once daily
<5	50 mg first dose, then 25 mg once daily

No additional dosing of lamivudine is required after routine (4 hour) hemodialysis or peritoneal dialysis.

Although there are insufficient data to recommend a specific dose adjustment of lamivudine in pediatric patients with renal impairment, a reduction in the dose and/or an increase in the dosing interval should be considered.

### **CONTRAINDICATIONS**

**LAMIVIR** Tablets and Oral Solution are contraindicated in patients with previously demonstrated clinically significant hypersensitivity (eg, anaphylaxis) to any of the components of the product.

### **WARNINGS AND PRECAUTIONS**

#### **Drug Interactions**

Lamivudine is predominantly eliminated in the urine 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 (eg, trimethoprim). No data are available regarding interactions with other drugs that have renal clearance mechanisms similar to that of lamivudine.

#### **Interferon- and Ribavirin-Based Regimens**

Although no evidence of a pharmacokinetic or pharmacodynamic interaction (eg, loss of HIV-1/HCV virologic suppression) was seen when ribavirin was co-administered with lamivudine in HIV/HCV co-infected patients, hepatic decompensation (some fatal) has occurred in HIV/HCV co-infected patients receiving combination antiretroviral therapy for HIV and interferon alfa with or without ribavirin (see **WARNINGS AND PRECAUTIONS**).

### **Zalcitabine**

Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another. Therefore, the use of lamivudine in combination with zalcitabine is not recommended.

### **Trimethoprim/Sulfamethoxazole (TMP/SMX)**

No change in the dose of either drug is recommended. There is no information regarding the effect on lamivudine pharmacokinetics of higher doses of TMP/SMX such as those used to treat PCP.

### **Drugs with No Observed Interactions with Lamivudine**

A drug interaction study showed no clinically significant interaction between lamivudine and zidovudine.

### **Lactic Acidosis/Severe Hepatomegaly with Steatosis**

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination, including lamivudine and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering lamivudine to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with lamivudine should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

### **Patients with HIV-1 and Hepatitis B Virus Co-infection**

#### ***Post-Treatment Exacerbations of Hepatitis***

In clinical trials in non-HIV-1-infected patients treated with lamivudine for chronic hepatitis B, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of lamivudine. These exacerbations have been detected primarily by serum ALT elevations in addition to the re-emergence of HBV DNA. Although most events appear to have been self-limited, fatalities have been reported in some cases. Similar events have been reported from postmarketing experience after changes from lamivudine-containing HIV-1 treatment regimens to non-lamivudine-containing regimens in patients infected with both HIV-1 and HBV. The causal relationship to discontinuation of lamivudine treatment is unknown. Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. There is insufficient evidence to determine whether re-initiation of lamivudine alters the course of post-treatment exacerbations of hepatitis.

### ***Important Differences Among Lamivudine-Containing Products***

**LAMIVIR** Tablets and Oral Solution contain a higher dose of the same active ingredient (lamivudine) than **LAMIVIR-HBV Tablets**. **LAMIVIR-HBV** was developed for patients with chronic hepatitis B. The formulation and dosage of lamivudine in **LAMIVIR-HBV** are not appropriate for patients co-infected with HIV-1 and HBV. Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients co-infected with HIV-1 and HBV. If treatment with **LAMIVIR-HBV** is prescribed for chronic hepatitis B for a patient with unrecognized or untreated HIV-1 infection, rapid emergence of HIV-1 resistance is likely to result because of the subtherapeutic dose and the inappropriateness of monotherapy HIV-1 treatment. If a decision is made to administer lamivudine to patients co-infected with HIV-1 and HBV, lamivudine should be used as part of an appropriate combination regimen.

#### ***Emergence of Lamivudine-Resistant HBV:***

In non-HIV-1-infected patients treated with lamivudine for chronic hepatitis B, emergence of lamivudine-resistant HBV has been detected and has been associated with diminished treatment response. Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been reported in HIV-1-infected patients who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus.

#### **Use with Other Lamivudine- and Emtricitabine-Containing Products**

Lamivudine should not be administered concomitantly with other lamivudine- or emtricitabine containing products.

#### **Use with Interferon- and Ribavirin-Based Regimens**

*In vitro* studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (eg, loss of HIV-1/HCV virologic suppression) was seen when ribavirin was co-administered with lamivudine in HIV-1/HCV co-infected patients (see **PHARMACOLOGY**), hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin. Patients receiving interferon alfa with or without ribavirin and lamivudine should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of lamivudine should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (eg, Childs Pugh >6).

#### **Pancreatitis**

In pediatric patients with a history of prior antiretroviral nucleoside exposure, a history of pancreatitis, or other significant risk factors for the development of

pancreatitis, lamivudine should be used with caution. Treatment with lamivudine should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur. (see **UNDESIRABLE EFFECTS**).

### **Immune Reconstitution Syndrome**

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including lamivudine. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

### **Fat Redistribution**

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and “cushingoid appearance”, have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

### **Renal Impairment**

Reduction of the dosage of lamivudine is recommended for patients with impaired renal function (see **DOSAGE AND ADMINISTRATION**).

### **Pregnancy**

#### ***Pregnancy Category C***

There are no adequate and well-controlled studies of lamivudine in pregnant women. Animal reproduction studies in rats and rabbits revealed no evidence of teratogenicity. Increased early embryoletality occurred in rabbits at exposure levels similar to those in humans. Lamivudine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lamivudine pharmacokinetics was studied in pregnant women during 2 clinical studies conducted in South Africa. The study assessed pharmacokinetics in 16 women at 36 weeks gestation using 150 mg lamivudine twice daily with zidovudine; 10 women at 38 weeks gestation using 150 mg lamivudine twice daily

with zidovudine; and 10 women at 38 weeks gestation using lamivudine 300 mg twice daily without other antiretrovirals. These studies were not designed or powered to provide efficacy information. Lamivudine pharmacokinetics in the pregnant women was similar to those seen in non-pregnant adults and in postpartum women. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples. In a subset of subjects, lamivudine amniotic fluid specimens were collected following the natural rupture of the membranes. Amniotic fluid concentrations of lamivudine were typically 2 times greater than maternal serum levels and ranged from 1.2 to 2.5 mcg/mL (150 mg twice daily) and 2.1 to 5.2 mcg/mL (300 mg twice daily).

It is not known whether the risk of adverse events associated with lamivudine are altered in pregnant women compared with other HIV-1-infected patients. Animal reproduction studies performed at oral doses up to 130 and 60 times the adult dose in rats and rabbits, respectively, revealed no evidence of teratogenicity due to lamivudine. Increased early embryoletality occurred in rabbits at exposure levels similar to those in humans. However, there was no indication of this effect in rats at exposure levels up to 35 times those in humans. Based on animal studies, lamivudine crosses the placenta and is transferred to the fetus.

### **Lactation**

The Centers for Disease Control and Prevention recommend that HIV-1 infected mothers do not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. Because of the potential for serious adverse reactions in nursing infants and HIV-1 transmission, mothers should be instructed not to breastfeed if they are receiving lamivudine.

Lamivudine is excreted in human milk. Samples of breast milk obtained from 20 mothers receiving lamivudine monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice daily and 300 mg zidovudine twice daily) had measurable concentrations of lamivudine.

### **Pediatric Use**

The safety and effectiveness of twice-daily lamivudine in combination with other antiretroviral agents have been established in pediatric patients, 3 months of age and older. (see **UNDESIRABLE EFFECTS AND PHARMACOLOGY**).

### **Geriatric Use**

Clinical studies of lamivudine did not include a sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. In particular, because lamivudine is

substantially excreted by the kidneys and elderly patients are more likely to have decreased renal function, renal function should be monitored and dosage adjustments should be made accordingly (see **DOSAGE AND ADMINISTRATION AND PHARMACOLOGY**).

### **UNDESIRABLE EFFECTS**

The following are the adverse reactions of lamivudine:

- Lactic acidosis and severe hepatomegaly with steatosis (see **BOXED WARNING, WARNINGS AND PRECAUTIONS**)
- Severe acute exacerbations of hepatitis B (see **BOXED WARNING, WARNINGS AND PRECAUTIONS**)
- Hepatic decompensation in patients co-infected with HIV-1 and Hepatitis C (see **WARNINGS AND PRECAUTIONS**)
- Pancreatitis (see **WARNINGS AND PRECAUTIONS**)

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

### **Adults**

The safety profile of lamivudine in adults is primarily based on 3,568 HIV-1 infected patients in 7 clinical trials. The most common adverse reactions are headache, nausea, malaise, fatigue, nasal signs and symptoms, diarrhea and cough.

Selected clinical adverse reactions of in  $\geq 5\%$  of patients during therapy with lamivudine 150 mg twice daily plus zidovudine 200 mg 3 times daily for up to 24 weeks are listed in Table 4.

**Table 4: Selected Clinical Adverse Events ( $\geq 5\%$  Frequency) in Four Controlled Clinical Trials (NUCA3001, NUCA3002, NUCB3001, NUCB3002)**

<b>Adverse Reaction</b>	<b>Lamivudine 150 mg twice daily plus Zidovudine (n = 251)</b>	<b>Zidovudine* (n = 230)</b>
<b>Body as a Whole</b>		
Headache	35%	27%
Malaise and fatigue	27%	23%
Fever or chills	10%	12%
<b>Digestive</b>		
Nausea	33%	29%
Diarrhea	18%	22%
Nausea and vomiting	13%	12%

Anorexia and/or decreased appetite	10%	7%
Abdominal pain	9%	11%
Abdominal cramps	6%	3%
Dyspepsia	5%	5%
<b>Nervous System</b>		
Neuropathy	12%	10%
Insomnia and other sleep disorders	11%	7%
Dizziness	10%	4%
Depressive disorders	9%	4%
<b>Respiratory</b>		
Nasal signs and symptoms	20%	11%
Cough	18%	13%
<b>Skin</b>		
Skin rashes	9%	6%
<b>Musculoskeletal</b>		
Musculoskeletal pain	12%	10%
Myalgia	8%	6%
Arthralgia	5%	5%

\*Either zidovudine monotherapy or zidovudine in combination with zalcitabine.

Pancreatitis was observed in 9 of the 2613 adult patients (0.3%) who received lamivudine in the controlled clinical trials EPV20001, NUCA3001, NUCB3001, NUCA3002, NUCB3002, and NUCB3007.(see **WARNINGS AND PRECAUTIONS**).

The types and frequencies of clinical adverse reactions reported in patients receiving lamivudine 300 mg once daily or lamivudine 150 mg twice daily (in 3-drug combination regimens in EPV20001 AND EPV40001) for 48 weeks were similar.

Selected laboratory abnormalities observed during therapy are summarized in Table 5.

**Table 5: Frequencies of Selected Grade 3–4 Laboratory Abnormalities in Adults in Four 24-Week Surrogate Endpoint Studies (NUCA3001, NUCA3002, NUCB3001, NUCB3002) and a Clinical Endpoint Study (NUCB3007)**

Test (Threshold Level)	24-Week Surrogate Endp-oint Studies*		Clinical Endpoint Study*	
	Lamivudine plus zidovudine	Zidovudine <sup>†</sup>	Lamivudine plus current therapy	Placebo plus current therapy <sup>‡</sup>
Absolute neutrophil count ( $<750/\text{mm}^3$ )	7.2%	5.4%	15%	13%
Hemoglobin ( $<8.0 \text{ g/dL}$ )	2.9%	1.8%	2.2%	3.4%
Platelets ( $<50,000/\text{mm}^3$ )	0.4%	1.3%	2.8%	3.8%
ALT ( $>5.0 \times$ ULN)	3.7%	3.6%	3.8%	1.9%
AST ( $>5.0 \times$ ULN)	1.7%	1.8%	4.0%	2.1%
Bilirubin ( $>2.5$ $\times$ ULN)	0.8%	0.4%	ND	ND
Amylase ( $>2.0$ $\times$ ULN)	4.2%	1.5%	2.2%	1.1%

\* The median duration on study was 12 months.

† Either zidovudine monotherapy or zidovudine in combination with zalcitabine.

‡ Current therapy was zidovudine, or zidovudine plus didanosine, or zidovudine plus zalcitabine.

ULN = Upper limit of normal.

ND = Not done.

The frequencies of selected laboratory abnormalities reported in patients receiving lamivudine 300 mg once daily or lamivudine 150 mg twice daily (in 3-drug combination regimens in EPV20001 and EPV40001) were similar.

### **Pediatric Patients**

Lamivudine Oral Solution has been studied in 638 pediatric patients 3 months to 18 years of age in 3 clinical trials.

Selected clinical adverse reactions and physical findings with a  $\geq 5\%$  frequency during therapy with lamivudine 4 mg/kg twice daily plus zidovudine 160 mg/m<sup>2</sup> three times daily in therapy-naive ( $\leq 56$  days of antiretroviral therapy) pediatric patients are listed in Table 6.

**Table 6: Selected Clinical Adverse Reactions and Physical Findings ( $\geq 5\%$  Frequency) in Pediatric Patients in Study ACTG300**

<b>Adverse Reaction</b>	<b>Lamivudine plus Zidovudine (n = 236)</b>	<b>Didanosine (n = 235)</b>
<b>Body as a Whole</b> Fever	25%	32%
<b>Digestive</b> Hepatomegaly Nausea and vomiting Diarrhea Stomatitis Splenomegaly	11% 8% 8% 6% 5%	11% 7% 6% 12% 8%
<b>Respiratory</b> Cough Abnormal breath sounds/wheezing	15% 7%	18% 9%
<b>Ear, Nose and Throat</b> Signs or symptoms of ears* Nasal discharge or congestion	7% 8%	6% 11%
<b>Other</b> Skin rashes Lymphadenopathy	12% 9%	14% 11%

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

#### **Pancreatitis**

Pancreatitis, which has been fatal in some cases, has been observed in antiretroviral nucleoside-experienced pediatric patients receiving lamivudine alone

or in combination with other antiretroviral agents. In an open-label, dose-escalation study (NUCA2002), 14 patients (14%) developed pancreatitis while receiving monotherapy with lamivudine. Three of these, 3 patients died of complications of pancreatitis. In a second open-label study (NUCA2005), 12 patients (18%) developed pancreatitis. In Study ACTG300, pancreatitis was not observed in 236 patients randomized to lamivudine plus zidovudine. Pancreatitis was observed in 1 patient in this study who received open-label lamivudine in combination with zidovudine and ritonavir following discontinuation of didanosine monotherapy (see **WARNINGS AND PRECAUTIONS**).

### **Paresthesias and Peripheral Neuropathies**

Paresthesias and peripheral neuropathies were reported in 15 patients (15%) in Study NUCA2002, 6 patients (9%) in Study NUCA2005, and 2 patients (<1%) in Study ACTG300.

Selected laboratory abnormalities experienced by therapy-naive ( $\leq 56$  days of antiretroviral therapy) pediatric patients are listed in Table 7.

**Table 7: Frequencies of Selected Grade 3–4 Laboratory Abnormalities in Pediatric Patients in Study ACTG300**

<b>Test (Threshold Level)</b>	<b>Lamivudine plus Zidovudine</b>	<b>Didanosine</b>
Absolute neutrophil count (<400/mm <sup>3</sup> )	8%	3%
Hemoglobin (<7.0 g/dL)	4%	2%
Platelets (<50,000/mm <sup>3</sup> )	1%	3%
ALT (>10 x ULN)	1%	3%
AST (>10 x ULN)	2%	4%
Lipase (>2.5 x ULN)	3%	3%
Total amylase (>2.5 x ULN)	3%	3%

ULN = Upper Limit of Normal

Limited short-term safety information is available from 2 small, uncontrolled studies in South Africa in neonates receiving lamivudine with or without zidovudine for the first week of life following maternal treatment starting at Week 38 or 36 of gestation.(see **PHARMACOLOGY**).Selected adverse reactions reported in these neonates included increased liver function tests, anemia, diarrhea, electrolyte

disturbances, hypoglycemia, jaundice and hepatomegaly, rash, respiratory infections, sepsis; 3 neonates died (1 from gastroenteritis with acidosis and convulsions, 1 from traumatic injury, and 1 from unknown causes). Two other non-fatal gastroenteritis or diarrhea cases were reported, including 1 with convulsions; 1 infant had transient renal insufficiency associated with dehydration. The absence of control groups limits assessments of causality, but it should be assumed that perinatally-exposed infants may be at risk for adverse events comparable to those reported in pediatric and adult HIV-infected patients treated with lamivudine-containing combination regimens. Long-term effects of *in utero* and infant lamivudine exposure are not known.

### **Observed During Clinical Practice**

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been reported during post-marketing use of lamivudine. Because these reactions are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These reactions have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to lamivudine.

***Body as a Whole:*** Redistribution/accumulation of body fat. (see **WARNINGS AND PRECAUTIONS**).

***Endocrine and Metabolic:*** Hyperglycemia.

***General:*** Weakness.

***Hemic and Lymphatic:*** Anemia (including pure red cell aplasia and severe anemias progressing on therapy),

***Hepatic and Pancreatic:*** Lactic acidosis and hepatic steatosis, post-treatment exacerbation of hepatitis B (see **BOXED WARNING, WARNINGS AND PRECAUTIONS**).

***Hypersensitivity:*** Anaphylaxis, urticaria.

***Musculoskeletal:*** Muscle weakness, CPK elevation, rhabdomyolysis.

***Skin:*** Alopecia, pruritus.

### **OVERDOSAGE**

There is no known antidote for lamivudine. One case of an adult ingesting 6 g of lamivudine was reported; there were no clinical signs or symptoms noted and hematologic tests remained normal. Two cases of pediatric overdose have been reported. One case involved was of a single dose of 7 mg/kg of lamivudine; the second case involved the use of 5 mg/kg of lamivudine twice daily for 30 days. There were no clinical signs or symptoms noted in either case. Because a

negligible amount of lamivudine was removed via 4-hour hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event. If overdose occurs, the patient should be monitored, and standard supportive treatment applied as required.

**PACKAGING INFORMATION**

**LAMIVIR-150 Tablets**.....Strip of 10 tablets

**LAMIVIR oral solution**.....Bottle of 100ml

*Last updated: October 2010*