PRODUCT MONOGRAPH

[Pr] Lamivudine oral solution

10 mg/mL as lamivudine

Antiretroviral agent

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Manufactured by:
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India.

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-medicinal Ingredients
Oral	Oral Solution/ 10 mg/mL	artificial strawberry and banana flavours, citric acid (anhydrous), methylparaben, propylparaben, propylene glycol, sodium citrate (dihydrate), sucrose and purified water

INDICATIONS AND CLINICAL USE

Lamivudine oral solution in combination with other antiretroviral agents is indicated for the treatment of HIV infection.

Pediatrics (< 18 years of age)

Lamivudine oral solution is indicated in pediatric patients aged 3 months and older in combination with other antiretroviral agents.

Geriatrics (≥ 65 years of age)

Clinical studies of lamivudine did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from younger patients. 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.

CONTRAINDICATIONS

- Lamivudine oral solution is contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of the products (see DOSAGE FORMS, COMPOSITION, AND PACKAGING section).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Lactic Acidosis and Severe Hepatomegaly with Steatosis**
  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, Hepatic/Biliary/Pancreatic).

- **Post-Treatment Exacerbations of Hepatitis B**
  Severe acute exacerbations of hepatitis B have been reported in patients who are infected with hepatitis B virus (HBV) 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. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

- **Pancreatitis in Pediatric Patients**
  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 ADVERSE REACTIONS section).

General

Lamivudine oral solution should not be administered concomitantly with other products containing lamivudine including HEPTOVIR® Tablets and Oral solution, COMBIVIR® Tablets, KIVEXA® Tablets, or TRIZIVIR® Tablets.

Lamivudine oral solution should also not be administered concomitantly with emtricitabine containing products, including ATRIPLA® Tablets, EMTRIVA® Capsules, TRUVADA® Tablets, COMPLERA® Tablets, or STRIBILD™ Tablets.

Evidence for once-daily dosing using the 300 mg dose is mainly in antiretroviral naive patients.

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

Patients should be advised that current antiretroviral therapy, including lamivudine, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Diabetic patients should be advised that an adult dose of lamivudine oral solution contains 3 g of sucrose.

Endocrine and Metabolism

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

Hematologic
Very rare occurrences of pure red cell aplasia have been reported with lamivudine use. Discontinuation of lamivudine has resulted in normalization of hematologic parameters in patients with suspected lamivudine-induced pure red cell aplasia.

Hepatic/Biliary/Pancreatic
Pancreatitis
Pancreatitis has been observed in some patients receiving nucleoside analogues, including 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.

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 (e.g., loss of HIV/HCV virologic suppression) was seen when ribavirin was coadministered 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. 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.

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 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 generalized weakness, anorexia and sudden unexplained weight loss, gastrointestinal symptoms and respiratory symptoms (dyspnea and tachypnea).

Caution should be exercised when administering lamivudine oral solution or other nucleoside analogues, particularly to those with known risk factors for liver disease. Treatment with

lamivudine oral solution 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).

Patients Co-infected with Hepatitis B virus
Clinical trials and marketed use of lamivudine oral solution 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 oral solution, which may have more severe consequences in patients with decompensated liver disease. If lamivudine oral solution 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.

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 (see full Product Monograph for HEPTOVIR® for additional information). 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.

Immune
Immune Reconstitution Inflammatory Syndrome
During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as MAC, CMV, PCP, and TB) which may necessitate further evaluation and treatment.

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.

Renal

Patients with Impaired Renal Function
Patients with impaired renal function may be at a greater risk of toxicity from lamivudine oral solution due to decreased renal clearance of the drug. Consideration should be given to appropriate reduction in the dose of lamivudine (see DOSAGE AND ADMINISTRATION section).

Special Populations

Pregnant Women
Lamivudine has not been studied in pregnant women. Therefore, lamivudine should not be used in pregnant women unless the potential benefits to the mother outweigh the potential risk to the fetus (see DETAILED PHARMACOLOGY).

There have been 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. Findings of developmental toxicity were also observed in animal toxicology studies (see TOXICOLOGY).

There have also 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.

Antiretroviral Pregnancy Registry
To monitor maternal-fetal outcomes of pregnant women exposed to ART (antiretroviral therapy), including lamivudine, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients:
http://www.apregistry.com
Telephone: (800) 258-4263
Fax: (800) 800-1052

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%. The Antiretroviral Pregnancy Registry does not show an increased risk of major birth defects for lamivudine compared to the background rate.

Nursing Women
HIV-1 infected mothers should not breast-feed their infants to avoid risking postnatal transmission of HIV. Lamivudine is excreted in breast milk at similar concentrations to those found in serum. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving lamivudine oral solution.**

Pediatrics
The safety and effectiveness of lamivudine have been established in pediatric patients aged 3 months and older. Use of lamivudine is supported by pharmacokinetic trials and evidence from adequate and well-controlled trials of lamivudine in adults and pediatric subjects (see **DOSAGE AND ADMINISTRATION – Recommended Dose and Dosage Adjustment, DETAILED PHARMACOLOGY, Pharmacokinetics in Pediatric Patients and CLINICAL TRIALS – Pediatric Subjects).**

Lower Virologic Suppression with Oral Solutions in Pediatrics
An all-tablet antiretroviral regimen should be used when possible. When an all-tablet regimen cannot be used, lamivudine oral solution may be used concomitantly with sorbitol-containing medicines only if the benefits of treatment outweigh possible risks, including lower virologic

suppression. Consider more frequent monitoring of HIV-1 viral load when lamivudine oral solution is used with chronically-administered, sorbitol-containing medicines (see **DRUG INTERACTIONS**).

Pediatric patients who received lamivudine oral solution concomitantly with other antiretroviral oral solutions at any time up to 96 weeks in the ARROW study had lower rates of virologic suppression, lower plasma lamivudine exposure, and developed viral resistance more frequently than those receiving lamivudine tablets (see DETAILED PHARMACOLOGY, pharmacokinetics in Pediatric Patients and MICROBIOLOGY, Resistance, Pediatrics). The proportion of subjects with HIV-1 RNA of less than 80 copies per mL through 96 weeks was higher in patients who had received tablet formulations (71% [213/301] and 74% [221/300]) than in those who had received any solution formulations (57% [17/30] and 50% [13/26] for once-daily and twice-daily dosing, respectively.

Geriatrics (> 65 years of age)
Clinical studies of lamivudine did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger patients. In general, caution should be exercised in the administration and monitoring of lamivudine oral solution in elderly patients, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labelling:

- Lactic acidosis and severe hepatomegaly (see WARNINGS AND PRECAUTIONS, Lactic Acidosis and Severe Hepatomegaly with Steatosis)
- Post-treatment exacerbations of hepatitis B (see WARNINGS AND PRECAUTIONS, Post-Treatment Exacerbations of Hepatitis B)
- Serum lipids and blood glucose (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism)
- Hepatic decompensation in patients co-infected with HIV-1 and Hepatitis C (see WARNINGS AND PRECAUTIONS, Use With Interferon and Ribavirin Based Regimens)
- Pancreatitis (see WARNINGS AND PRECAUTIONS, Pancreatitis; and WARNINGS AND PRECAUTIONS, Pancreatitis is Pediatric Patients)

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adults
Selected clinical adverse events in therapy-naive patients receiving either lamivudine 300 mg once daily or lamivudine 150 mg twice daily in combination with zidovudine 300 mg twice daily and efavirenz 600 mg once daily are listed in Table 1 and Table 2. The most frequent clinical adverse events (≥ 5% frequency) reported during therapy with lamivudine 150 mg b.i.d. plus zidovudine 600 mg per day compared with zidovudine are listed in Table 3.

Table 1: Most Common Adverse Events (> 10%)[a] Occurring in Subjects in EPV20001 Safety Population during 48 Weeks

Adverse Event	Lamivudine 300 mg q.d. plus Zidovudine plus Efavirenz (n = 272)	Lamivudine 150 mg b.i.d. plus Zidovudine plus Efavirenz (n = 273)
At Least One Adverse Event	94%	97%
Nausea	39%	44%
Dizziness	30%	36%
Fatigue	31%	31%
Dreams	26%	24%
Headaches	25%	22%
Rashes	24%	20%
Viral respiratory infections	22%	21%
Diarrhea	20%	21%
Ear, nose, & throat infections	15%	21%
Sleep disorders	17%	19%
Vomiting	14%	16%
Abdominal pain	10%	19%
Anorexia	13%	9%
Mood disorders	12%	10%
Musculoskeletal pain	7%	14%
Sinus disorders	9%	10%
Fever	7%	12%

[a] >10% of subjects in either treatment group.

Table 2: Severe Adverse Events (Grade 3/4) Occurring in More Than One Subject[a] in EPV20001 Safety Population during 48 Weeks

Adverse Event	Lamivudine 300 mg q.d. plus Zidovudine plus Efavirenz (n = 272)	Lamivudine 150 mg b.i.d. plus Zidovudine plus Efavirenz (n = 273)
At Least One Severe Adverse Event	24%	26%
Increased creatine phosphokinase levels	3%	4%
Nausea	3%	3%
Increased liver function tests	2%	3%
Decreased white cells	2%	2%
Fatigue	1%	2%
Hypertriglyceridemia	2%	1%
Dizziness	1%	1%
Vomiting	1%	<1%
Sleep disorders	1%	1%
Abdominal pain	1%	<1%
Dreams	<1%	1%
Increased amylase levels	1%	<1%
Anxiety	1%	<1%
Rashes	0%	2%
Anemia	<1%	1%
Depressive disorders	<1%	1%
Mood disorders	1%	<1%
Skin infections	<1%	<1%
Ear, nose, & throat infections	<1%	<1%
Diarrhea	<1%	<1%
Headaches	<1%	<1%
Suicide & attempted suicide	<1%	<1%
Viral respiratory infections	<1%	<1%
Confusion	<1%	<1%
Migraines	<1%	<1%
General signs & symptoms	<1%	<1%
Malaise	0%	<1%
Viral Infection	<1%	0%
Lower respiratory infections	<1%	<1%
Hypotension	0%	<1%

[a] more than one subject in any treatment group.

Table 3: Most Frequent Clinical Adverse Events (≥ 5% Frequency) Reported in Four Controlled Clinical Trials (NUCA3001, NUCA3002, NUCB3001 and NUCB3002)

Adverse Event	Lamivudine 150 mg b.i.d. plus Zidovudine (n = 251)	Zidovudine (n = 230)
Body as a whole		
Headache	35%	27%
Malaise and fatigue	27%	23%
Fever or chills	10%	12%
Digestive		
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%
Nervous		
Neuropathy	12%	10%
Dizziness	10%	7%
Insomnia & other sleep disorders	11%	4%
Depressive disorders	9%	4%
Respiratory		
Nasal signs & symptoms	20%	11%
Cough	18%	13%
Skin & appendages		
Skin rashes	9%	6%
Musculoskeletal		
Musculoskeletal pain	12%	10%
Myalgia	8%	6%
Arthralgia	5%	5%

Other clinical adverse events reported in controlled clinical trials in association with lamivudine 150 mg b.i.d. plus zidovudine 600 mg per day in at least 1% of patients were:

Gastrointestinal: abdominal discomfort and pain (3%), abdominal distension (3%), dyspepsia (2%), gastrointestinal discomfort and pain (3%), gastrointestinal gas (4%), hyposalivation (2%), oral ulceration (1%)

Musculoskeletal: muscle atrophy/weakness/tiredness (1%), muscle pain (2%)

Neurological: mood disorders (1%), sleep disorders (4%), taste disturbances (1%)

Other: breathing disorders (2%), general signs and symptoms (1%), pain (2%), sexual function disturbances (1%), temperature regulation disturbance (1%)

Skin: pruritis (1%), skin rashes (1%), sweating (1%)

Pancreatitis was observed in 9 of 2613 adult patients (0.3%) in controlled clinical trials EPV20001, NUCA3001, NUCB3001, NUCA3002, NUCB3002, and NUCB3007.

Six percent (6%) of patients treated with lamivudine 150 mg b.i.d. plus zidovudine 200 mg t.i.d. in controlled clinical trials permanently discontinued treatment due to an investigator-attributed drug-related adverse event, compared with 7% of patients receiving monotherapy with zidovudine and 13% of patients receiving zidovudine plus zalcitabine. The most frequent adverse events necessitating such permanent discontinuation of therapy with lamivudine 150 mg b.i.d. plus zidovudine 200 mg t.i.d. were nausea (2%), malaise and fatigue (1%), and anemia (1%).

The frequencies of selected laboratory abnormalities (Grades 3 and 4) during therapy are listed in Table 4.

Table 4: Selected Laboratory Abnormalities in Studies of Lamivudine in Adults

Test (Abnormal Level)	24-Week Surrogate Endpoint Studies (NUCA3001, NUCA3002, NUCB3001, NUCB3002)		Clinical Endpoint Study* (NUCB3007)		Study EPV20001*	
	Lamivudine plus Zidovudine	Zidovudine	Lamivudine plus current therapy†	Placebo plus current therapy†	Lamivudine 300 mg q.d.♠	Lamivudine 150 mg b.i.d.♠
Neutropenia (ANC<750/mm^3)	7%	5%	15%	13%	6%	6%
Anemia (Hgb<8.0g/dL)	3%	2%	2%	3%	<1%	<1%
Thrombocytopenia (platelets<50000/mm^3)	<1%	1%	3%	4%	0%	<1%
ALT (>5.0 × ULN)	4%	4%	4%	2%	3%	5%
AST (>5.0 × ULN)	2%	2%	4%	2%	2%	4%
Bilirubin (>2.5 × ULN)	<1%	<1%	ND	ND	0%	<1%
Amylase (>2.0 × ULN)	4%	2%	2%	1%	3%	2%

*The median duration on study was 12 months.
†Current therapy was either zidovudine, zidovudine plus didanosine, or zidovudine plus zalcitabine.
♠Therapy was lamivudine plus zidovudine plus efavirenz.
ULN = Upper limit of normal
ANC = Absolute neutrophil count
ND = Not done

Pediatric Patients

Selected clinical adverse events and physical findings with a ≥ 5% frequency during therapy with lamivudine 4 mg/kg twice daily plus zidovudine 160 mg/m^2 three times daily compared with didanosine in patients without, or with, minimal (≤ 56 days) prior antiretroviral therapy are listed in Table 5.

Table 5: Selected Clinical Adverse Events and Physical Findings (≥ 5% Frequency) in Pediatric Patients in Study ACTG300

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

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

Selected laboratory abnormalities experienced by patients without or minimal (≤ 56 days) prior antiretroviral therapy are listed in Table 6.

Table 6: Frequencies of Selected Laboratory Abnormalities in Pediatric Patients in Study ACTG300

Test (Abnormal Level)	Lamivudine plus Zidovudine	Didanosine
Neutropenia (ANC<400/mm^3)	8%	3%
Anemia (Hgb<7.0 g/dL)	4%	2%
Thrombocytopenia (platelets<50,000/mm^3)	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.
ANC = Absolute neutrophil count.

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 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 one patient in this study who received open-label lamivudine in combination with zidovudine and ritonavir following discontinuation of didanosine monotherapy.

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

Once-Daily Dosing (ARROW: COL105677)
The safety of once-daily compared with twice-daily dosing of lamivudine was assessed in the ARROW trial. 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. 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.

Post-Market Adverse Drug Reactions
The following additional adverse experiences have been reported in post-marketing experience without regard to causality. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, potential causal connection to lamivudine, or a combination of these factors.

Body as a whole:	anaphylaxis, fatigue, fever, malaise, weakness
Digestive:	stomatitis
Endocrine/Metabolic:	hyperglycemia, hyperlactatemia, lactic acidosis and hepatic steatosis (see WARNINGS AND PRECAUTIONS section)
Gastrointestinal:	diarrhea, nausea, pancreatitis, rises in serum amylase, upper abdominal pain, vomiting
Hematological:	pure red cell aplasia
Hepatic:	transient rises in liver enzymes
Hemic and Lymphatic:	anemia, lymphadenophathy, neutropenia, splenomegaly, thrombocytopenia

Immune System:	Immune Reconstitution Inflammatory Syndrome (see WARNINGS AND PRECAUTIONS: Immune section)
Musculoskeletal:	arthralgia, muscle disorders including very rarely rhabdomyolysis
Nervous:	headache, paresthesia, peripheral neuropathy
Other:	alopecia
Skin:	pruritus, rash, urticaria

DRUG INTERACTIONS

Overview

Lamivudine is predominantly eliminated by active organic cationic secretion.
The possibility of interactions with other drugs administered concurrently should be considered, particularly when the main route of elimination is renal.

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 Pglycoprotein (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 μM, 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 coadministration of drugs that are inhibitors of these efflux transporters is unlikely to affect the disposition and elimination of lamivudine.

Drug-Drug Interactions

Table 7: Established or Potential Drug-Drug Interactions

Proper name	Effect	Clinical comment
Emtricitabine	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.
Sorbitol	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 of 14%, 32%, and 36% in lamivudine exposure (AUC_{∞}) and 28%, 52%, and 55% in the C_{max} of lamivudine in adults.	When possible, avoid use of lamivudine with sorbitol-containing medicines or consider more frequent monitoring of HIV-1 viral load when chronic coadministration cannot be avoided (see Warnings and Precautions).
Trimethoprim	Administration of trimethoprim, a constituent of co-trimoxazole, causes a 40% increase in lamivudine plasma levels.	However, unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary. Lamivudine has no effect on the pharmacokinetics of co-trimoxazole. Administration of co-trimoxazole with the lamivudine/zidovudine combination in patients with renal impairment should be carefully assessed. The effect of co-administration of lamivudine with higher doses of co-trimoxazole for the treatment of *Pneumocystis jiroveci* pneumonia (also referred to as PCP) and toxoplasmosis has not been studied.
Zidovudine	Zidovudine has no effect on the pharmacokinetics of lamivudine (see ACTIONS AND CLINICAL PHARMACOLOGY section)	A modest increase in Cmax (28%) was observed for zidovudine when administered with lamivudine, however overall exposure (AUC) was not significantly altered. Zidovudine plasma levels are not significantly altered when coadministered with lamivudine oral solution.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbs have not been established.

Drug-Laboratory Test Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Lamivudine therapy should be initiated by a physician experienced in the management of HIV infection.

Recommended Dose and Dosage Adjustment

Lamivudine can be taken with or without food.

Adults, Adolescents and Children weighing at least 25 kg
The recommended oral dose of lamivudine oral solution for adults and adolescents weighing at least 25 kg is 300 mg daily, administered as either 150 mg twice daily or 300 mg once daily (see ACTIONS AND CLINICAL PHARMACOLOGY, WARNINGS AND PRECAUTIONS and CLINICAL TRIALS section).

Pediatric patients (aged ≥ 3 months and weighing less than 25 kg)
The recommended oral dose of lamivudine oral solution for pediatric patients is 4 mg/kg twice daily (up to a maximum of 150 mg twice a day) or 8 mg/kg once daily (up to a maximum of 300 mg once daily) (see WARNINGS AND PRECAUTIONS, Lower Virologic Suppression with Oral Solutions in Pediatrics).

Pediatric patients less than 3 months of age:
The limited data available are insufficient to propose specific dosage recommendations (see Pharmacokinetics in Pediatric Patients).

Dose Adjustment
Patients with impaired renal function have increases in C_{max} and half-life of lamivudine with diminishing creatinine clearance. In addition, apparent total oral clearance of lamivudine decreases as creatinine clearance decreases. Doses of lamivudine oral solution may be adjusted, as shown in Table 8 and Table 9, in accordance with creatinine clearance.

No dose adjustment is necessary in patients with moderate or severe hepatic impairment unless accompanied by renal impairment.

Table 8: Adjustment of Dosage of Lamivudine Oral Solution in Accordance With Creatinine Clearance in Adults, Adolescents and Children weighing ≥25 kg

Creatinine clearance (mL/min)	Recommended Dosage of lamivudine oral solution
≥ 50	150 mg twice daily or 300 mg once daily
30 - 50	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

Table 9: Adjustment of Dosage of lamivudine in Accordance with Creatinine Clearance in Children aged ≥3 months and weighing less than 25 kg

Creatinine clearance (mL/min)	Recommended Dosage of Lamivudine
30 - 50	4 mg/kg once daily
15 - 29	4 mg/kg first dose then 2.6 mg/kg once daily
5 - 14	4 mg/kg first dose then 1.3 mg/kg once daily
< 5	1.3 mg/kg first dose then 0.7 mg/kg once daily

Missed Dose

If you forget to take your medicine, take it as soon as you remember. Then continue as before.

OVERDOSAGE

For management of a suspected drug overdose, please contact your regional Poison Control Centre immediately.

If overdosage occurs the patient should be monitored, and standard supportive treatment applied as required.

Administration of activated charcoal may be used to aid in the removal of unabsorbed active substance. General supportive measures are recommended.

Since lamivudine is dialyzable, continuous hemodialysis could be used in the treatment of overdose, although this has not been studied.

Limited data are available on the consequences of ingestion of acute overdoses in humans. No fatalities occurred, and the patients recovered. No specific signs or symptoms have been

identified following such overdose.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Lamivudine is a synthetic nucleoside analogue, an (-) enantiomer of a dideoxy analogue of cytidine. The sugar ring of lamivudine is novel in that it contains a sulphur at the 3´ position as a second heteroatom. Lamivudine is metabolized by intracellular kinases to its triphosphate (TP), which is the active moiety (lamivudine triphosphate or L-TP) Lamivudine is a nucleoside reverse transcriptase inhibitor (NRTI), and is a potent, selective inhibitor of HIV-1 and HIV-2 replication in vitro. In vitro L-TP has an intracellular half-life of approximately 10.5 to 15.5 hours. L-TP is a substrate for and a competitive inhibitor of HIV reverse transcriptase (RT). Inhibition of RT is via viral DNA chain termination after nucleoside analogue incorporation. L-TP shows significantly less affinity for host cell DNA polymerases and is a weak inhibitor of mammalian α, β, and γ DNA polymerases.

Pharmacokinetics

The pharmacokinetic properties of lamivudine have been studied in asymptomatic, HIV-infected adult patients after administration of single oral, multiple oral and intravenous (IV) doses ranging from 0.25 to 10 mg/kg. After oral administration of 2 mg/kg, the peak plasma lamivudine concentration (C_{max}) was 1.5 ± 0.5 µg/mL (mean ± S.D.) and half-life was 2.6 ± 0.5 hours. There were no significant differences in half-life across the range of single doses (0.25 to 8 mg/kg). The area under the plasma concentration versus time curve (AUC) and C_{max} increased in proportion to dose over the range from 0.25 to 10 mg/kg.

The steady-state pharmacokinetic properties of the lamivudine 300 mg tablet once daily for 7 days compared to 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 to 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 to the 150 mg twice-daily regimen.

The clinical significance of observed differences for both plasma lamivudine concentrations and intracellular lamivudine triphosphate concentrations is not known.

Lamivudine is well absorbed from the gut, and the bioavailability of oral lamivudine in adults is normally between 80 and 85%. Following oral administration, the mean time (t_{max}) to maximal serum concentrations (C_{max}) is about an hour. Absorption differences have been observed between adult and pediatric populations (see **DETAILED PHARMACOLOGY, Special Populations and Conditions, Pharmacokinetics in Pediatric Patients**).

No dose adjustment is needed when coadministered with food as lamivudine bioavailability is not altered, although a delay in t_{max} and reduction in C_{max} have been observed. Lamivudine exhibits

linear pharmacokinetics over the therapeutic dose range and displays limited binding to the major plasma protein albumin.

Coadministration of zidovudine results in a 13% increase in AUC_{∞} for zidovudine and a 28% increase in peak plasma levels. This is not considered to be of significance to patient safety and therefore no dosage adjustments are necessary.

STORAGE AND STABILITY

Lamivudine oral solution 10mg/mL should be stored between 15 – 25°C.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Lamivudine oral solution is a colourless to pale yellow, strawberry-banana flavoured, clear liquid containing 10 mg of lamivudine in each 1 mL. Nonmedicinal ingredients contained therein include banana flavor, citric acid, methylparaben, propylene glycol, propylparaben, purified water, sodium citrate, strawberry flavor and sucrose. Available in quantity of 240 mL (300mL HDPE bottles).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

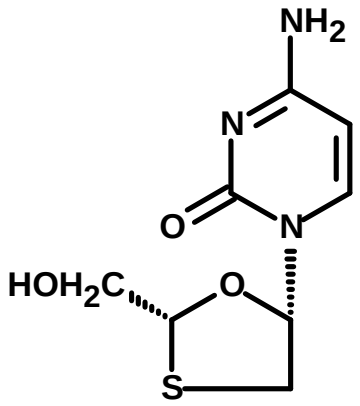
Drug Substance

Proper name: Lamivudine

Chemical name: 2(1H)-Pyrimidinone, 4-amino-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-,(2R-cis)

Molecular formula and molecular mass: $C_8H_{11}N_3O_3S$ 229.26 g/mol

Structural formula:



Physicochemical properties:

Description: Lamivudine is a white to off-white solid with a melting range of 173 to 179°C.

Solubility:

Solvent	Temperature (°C)	Solubility (mg/mL)
Water	25	134.08
Methanol	25	10.00
Dichloromethane	25	Practically insoluble
n-Hexane	25	Practically insoluble

pKa and pH: The pH value of a 1% w/v solution in water is approximately 6.9. The pKa determined by UV is 4.30.

CLINICAL TRIALS

Clinical Endpoint Study in Adults

NUCB3007 (CAESAR) was a multicentre, double-blind, placebo-controlled study comparing continued current therapy [zidovudine alone (62% of patients) or zidovudine with didanosine or zalcitabine (38% of patients)] to the addition of lamivudine or lamivudine plus an investigational non-nucleoside reverse transcriptase inhibitor, randomized 1:2:1. A total of 1816 HIV-infected adults with 25 to 250 CD4 cells/mm^3 (median = 122 cells/mm3) at baseline were enrolled: median age was 36 years, 87% were male, 84% were nucleoside-experienced, and 16% were therapy-naive. The median duration on study was 12 months. Results are summarized in Table 10.

Table 10: Number of Patients (%) With At Least One HIV Disease Progression Event or Death

Endpoint	Current Therapy (n = 460)	Lamivudine plus Current Therapy (n = 896)	Lamivudine plus a NNRTI* plus Current Therapy (n = 460)
HIV progression or death	90 (19.6%)	86 (9.6%)	41 (8.9%)
Death	27 (5.9%)	23 (2.6%)	14 (3.0%)

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

Surrogate Endpoint Study in Therapy-Naive Adults

EPV20001 is a multicentre, double-blind, placebo-controlled study in which patients were randomized 1:1 to receive lamivudine 300 mg once daily or lamivudine 150 mg twice daily in combination with zidovudine 300 mg twice daily and efavirenz 600 mg once daily. A total of 554 antiretroviral treatment-naive HIV-infected adults enrolled: male (79%), Caucasian (50%), median age of 35 years, baseline CD4 cell counts of 69 to 1089 cells/mm3 (median = 362 cells/mm3), and median baseline plasma HIV RNA of 4.66 log10 copies/mL. Percentages of patients with HIV RNA < 400 copies/mL and outcomes of treatment through are summarized in Table 11.

Table 11: Outcomes of Randomized Treatment through 48 weeks (Intent-to Treat)

Outcome	Lamivudine 300 mg q.d. plus Zidovudine plus Efavirenz (n = 278)	Lamivudine 150 mg b.i.d. plus Zidovudine plus Efavirenz (n = 276)
HIV RNA < 400 copies/mL	64%	63%
HIV RNA ≥ 400 copies/mL*	2%	2%
Discontinued due to clinical progression	< 1%	0%
Discontinued due to adverse events	6%	12%
Discontinued due to protocol defined virologic failure	2%	2%
Discontinued due to insufficient viral load response	1%	< 1%
Discontinued due to other reasons◊	24%	20%

*Includes HIV RNA measurements collected after discontinuation of study medication.
◊Includes consent withdrawn, lost to follow up, protocol violation, data outside the study-defined schedule, and randomized but never initiated treatment

In patients receiving lamivudine 300 mg once daily, the proportion of patients with HIV RNA < 400 copies/mL at Week 48 was similar for patients with baseline HIV RNA > 100,000 copies/mL (68%) and patients with baseline HIV RNA ≤ 100,000 copies/mL (62%). In patients receiving lamivudine twice daily, the proportion of patients with HIV RNA < 400 copies/mL at week 48 was 53% for patients with baseline HIV-RNA > 100,000 copies/mL and 67% in patients with baseline HIV RNA ≤ 100,000 copies/mL. The proportion of patients with HIV RNA < 50 copies/mL (via Roche Ultrasensitive assay) at Week 48 were similar between patients receiving lamivudine 300 mg once daily (61%) and patients receiving lamivudine 150 mg twice daily (62%). Similar increases in median CD4+ cell counts were observed at Week 48 in patients receiving lamivudine 300 mg once daily (144 cells/mm^3) and patients receiving lamivudine 150 mg twice daily (146 cells/mm^3).

Clinical Endpoint Study in Pediatric Patients

ACTG300 was a multicentre, randomized, double-blind study that provided for comparison of lamivudine plus zidovudine to didanosine monotherapy. A total of 471 symptomatic, HIV-infected pediatric patients, without, or with, minimal (≤ 56 days) prior antiretroviral therapy, were enrolled in these two treatment arms. The median age was 2.7 years (range 6 weeks to 14 years), 58% were female, and 86% were non-Caucasian. The mean baseline CD4 cell count was 868 cells/mm^3 (mean: 1060 cells/mm^3 and range: 0 to 4650 cells/mm3 for patients > 5 years of age; mean: 419 cells/mm^3 and range: 0 to 1555 cells/mm^3 for patients > 5 years of age) and the mean baseline plasma HIV RNA was 5.0 log10 copies/mL. The median duration on study was 10.1 months for the patients receiving lamivudine plus zidovudine and 9.2 months for patients receiving didanosine monotherapy. Results are summarized in Table 12.

Table 12: Number of Patients (%) Reaching a Primary Clinical Endpoint (Disease Progression or Death)

Endpoint	Lamivudine plus Zidovudine (n = 236)	Didanosine (n = 235)
HIV disease progression or death (total)	15 (6.4%)	37 (15.7%)
Physical growth failure	7 (3.0%)	6 (2.6%)
Central nervous system deterioration	4 (1.7%)	12 (5.1%)
CDC Clinical Category C	2 (0.8%)	8 (3.4%)
Death	2 (0.8%)	11 (4.7%)

Once-Daily Dosing

ARROW (COL105677) was a 5-year randomized, multicenter trial which evaluated multiple aspects of clinical management of HIV-1 infection in pediatric patients. HIV-1 infected, treatment-naive subjects aged 3 months to 17 years were enrolled and treated with first-line regimen containing lamivudine and abacavir, dosed twice daily according to World Health Organization recommendations. After 36 weeks on treatment, subjects were given the option to participate in Randomization 3 of the ARROW trial, comparing the safety and efficacy of once-daily with twice-daily dosing of lamivudine and abacavir, in combination with a third antiretroviral drug for an additional 96 weeks.

Of the 1206 original subjects enrolled in the study, 669 participated in Randomization 3. Virologic suppression was not a requirement for participation: at baseline (following a minimum of 36 weeks of twice-daily treatment), 76% of subjects in the twice-daily cohort were virologically suppressed, compared with 71% of subjects in the once-daily cohort.

The proportion of subjects with HIV-1 RNA of less than 80 copies per mL through 96 weeks is shown in Table 14. The differences between virologic responses in the two treatment arms were comparable across baseline characteristics for gender and age.

Table 13: Proportions of Responders by HIV-1 RNA Copies Through 96 Weeks (From Randomization to Once-Daily or Twice-Daily Dosing - Snapshot Analysis)

	Lamivudine plus abacavir Twice Daily Dosing n = 333 N (%)	**Lamivudine plus abacavir Once Daily Dosing n= 336 N (%)**
Week 0 (After ≥36 Weeks on Treatment)		
Virological Response (<80 copies/mL)	250 (75)	237 (71)
Risk difference	-4.5% (95% CI - 11.3% to +2.2%)	
Week 48		
Virological Response (<80 copies/mL)	242 (73)	233 (69)
Risk difference	3.3% (95% CI - 10.2% to +3.5%)	
Week 96		
Virological Response (<80 copies/mL)	232 (70)	226 (67)
Risk difference	-2.4% (95% CI - 9.4% to +4.6%)	

The lamivudine plus abacavir once daily dosing group demonstrated non-inferiority to the twice daily group according to the pre-specified non-inferiority margin of -12%, for the primary endpoint of <80 c/mL at Week 48 and including Week 96 (the secondary endpoint) for all other thresholds tested (<200c/mL, <400c/mL, <1000c/mL). Virologic outcomes between treatment arms were comparable across baseline characteristics (gender, age, or viral load at randomization).

DETAILED PHARMACOLOGY

Pharmacokinetics in Adults

The pharmacokinetic properties of lamivudine have been studied in asymptomatic, HIV infected adult patients after administration of single oral and intravenous (IV) doses ranging from 0.25 to 8 mg/kg. Patients receiving multiple doses of 150 or 300 mg b.i.d. have also been studied.

Absorption and Bioavailability

Lamivudine was rapidly absorbed after oral administration in HIV-infected patients. After oral administration of 2 mg/kg to nine adults with HIV, the peak plasma lamivudine concentration (C_{max}) was 1.5 ± 0.5 μg/mL (mean ± S.D.). The area under the plasma concentration versus time curve (AUC) and C_{max} increased in proportion to dose over the range from 0.25 to 10 mg/kg. Absolute bioavailability in 12 adult patients was 87% ± 13% for the oral solution.

Lamivudine was administered orally to 12 asymptomatic, HIV-infected patients on two occasions, once in the fasted state and once with food. There was no significant difference in systemic exposure (AUC) in the fed and fasted states; therefore, lamivudine oral solution may be

administered with or without food. Absorption was slower in the fed state as shown by a 47% reduction in mean C_{max} from fasted values and a prolonged time to peak concentration.

Distribution
The apparent volume of distribution after IV administration of lamivudine was 1.3 ± 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 concentration-dependent, with 36% bound at 0.1 µg /mL and less than 10% bound at concentrations ≥ 1 mcg/mL. The distribution of lamivudine in whole human blood was studied *in vitro*. Over the concentration range of 0.1 to 100 µg /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 which accounts for less than 5% of an oral 150 mg dose of lamivudine. Glucuronide conjugation has not been observed as a metabolic pathway for lamivudine in man.

Elimination
The majority of lamivudine is eliminated unchanged in urine. Within 4 hours after a single oral dose, 71% ± 16% (mean ± S.D.) of the dose is excreted unchanged in urine. Total clearance and terminal elimination half-life were independent of dose and body weight over an oral dosing range from 0.25 to 10.0 mg/kg.

In most single-dose studies in HIV-infected patients, the observed mean elimination half-life ($T_{½}$) ranged from 5 to 7 hours. In one study with extended blood sampling, the mean elimination half-life was 11.9 hours.

Special Populations and Conditions

Adults With Impaired Renal Function
The pharmacokinetic properties of lamivudine were determined in a small group of HIV-infected adults with impaired renal function, and are summarized in Table 14.

Table 14: Pharmacokinetic Parameters (Mean ± S.D.) After a Single 300 mg Oral Dose of Lamivudine in Three Groups of Adults With Varying Degrees of Renal Function (CrCl > 60 mL/min, CrCl = 10-30 mL/min, and CrCl < 10 mL/min)

Number of subjects	6	4	6
Creatinine clearance criterion	>60 mL/min	10-30 mL/min	<10 mL/min
Creatinine clearance (mL/min)	111 ± 14	28 ± 8	6 ± 2
C_{max} (µg/mL)	2.6 ± 0.5	3.6 ± 0.8	5.8 ± 1.2
AUC_{∞} (µg·h/mL)	11.0 ± 1.7	48.0 ± 19	157 ± 74
Cl/F (mL/min)	464 ± 76	114 ± 34	36 ± 11

These results show increases in C_{max} and half-life with diminishing creatinine clearance. Apparent total clearance (Cl/F) of lamivudine decreased as creatinine clearance decreased. T_{max} was not significantly affected by renal function. Based on these observations, it is recommended that the dosage of lamivudine be modified in patients with reduced creatinine clearance (see DOSAGE AND ADMINISTRATION section).

Drug Interactions

The likelihood of adverse drug interactions with lamivudine is low due to limited metabolism and plasma protein binding and almost complete renal clearance. Coadministration of zidovudine results in a 13% increase in AUC_{∞} for zidovudine and a 28% increase in peak plasma levels. While statistically significant, these results are not considered to be clinically significant with respect to patient safety. Therefore, no dosage adjustments are necessary.

An interaction with trimethoprim, a constituent of co-trimoxazole, causes a 40% increase in lamivudine AUC_{∞} at therapeutic doses. This does not require dose adjustment unless the patient also has renal impairment (see DOSAGE AND ADMINISTRATION section).

Pharmacokinetics in Pediatric Patients

The pharmacokinetics of lamivudine have been studied after either single or repeat doses of lamivudine in 210 pediatric subjects. Pediatric subjects receiving lamivudine oral solution according to the recommended dosage regimen achieved approximately 25% lower plasma concentrations of lamivudine compared with HIV-1 infected adults. Pediatric subjects receiving lamivudine oral tablets according to the recommended dosage regimen achieved plasma concentrations of lamivudine similar to adults. Subjects receiving lamivudine oral tablets achieved higher plasma concentrations of lamivudine than subjects receiving oral solution because the weight-band–based dosing for the tablet formulation results in administration of higher mg/kg doses due to higher bioavailability of the tablets. The absolute bioavailability of both lamivudine tablet and oral solution are lower in children than adults.

The pharmacokinetics of lamivudine dosed once daily in HIV-1-infected pediatric patients aged 3 months through 12 years was evaluated in 3 studies (PENTA-15 [n=17], PENTA-13 [n=19], and ARROW PK [n=35]). These 3 studies were designed as 2 –period, crossover, open-label pharmacokinetic studies of twice-versus once-daily dosing of abacavir and lamivudine. These 3 studies demonstrated that once-daily dosing provides equivalent AUC0-24 to twice-daily dosing of lamivudine at the same total daily dose for both the oral solution and tablet formulations. The mean Cmax was approximately 80% to 90% higher with lamivudine once-daily dosing compared with twice-daily dosing.

Table 15: Pharmacokinetic Parameters (Geometric Mean [95% CI]) after Repeat Dosing of Lamivudine in 3 Pediatric 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.

Distribution of lamivudine into cerebrospinal fluid was assessed in 38 pediatric patients. Cerebrospinal fluid concentrations were 3% to 47% of the concentration in a simultaneous serum sample. The true extent of penetration of relationship with any clinical efficacy is unknown.

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

MICROBIOLOGY

Virology
Lamivudine is a potent inhibitor of HIV-1 and HIV-2 *in vitro*. Intracellularly, lamivudine is phosphorylated to its active 5'-triphosphate metabolite (lamivudine triphosphate or L-TP), which has an intracellular half-life of approximately 10.5 to 15.5 hours. The principal mode of action of lamivudine is inhibition of HIV reverse transcription via viral DNA chain termination. In addition, L-TP inhibits both the RNA- and DNA-dependent DNA polymerase activities of reverse transcriptase (RT), and is a weak inhibitor of mammalian α, β, and γ DNA polymerases. Lamivudine does not act as a chain terminator of mitochondrial DNA synthesis. Lamivudine has little effect on mammalian cell mitochondrial DNA content and does not interfere with normal cellular deoxynucleotide metabolism (*in vitro*).

***In Vitro* Activity**
The relationships between *in vitro* susceptibility of HIV to lamivudine and the inhibition of HIV replication in humans or clinical response are still being investigated. The anti-HIV activity of nucleoside analogues *in vitro* can vary depending on the viral strain, cell type, and assay used to measure such activity. To assess the activity of lamivudine, a number of virus/cell combinations were used, and inhibitory activity was measured in different assays by determination of IC_{50} and IC_{90} values. Lamivudine demonstrated anti-HIV-1 and anti-HIV-2 activities in all virus/cell combinations tested.

The antiviral activity of lamivudine has been studied in combination with other antiretroviral compounds using HIV-1-infected MT-4 cells as the test system. No antagonistic effects were seen in vitro with lamivudine and other antiretrovirals (tested agents: abacavir, didanosine, nevirapine, zalcitabine, and zidovudine).

Resistance
In nonclinical studies, lamivudine-resistant isolates of HIV have been selected *in vitro*. A known mechanism of lamivudine resistance is the change in the 184 amino acid of RT from methionine to either isoleucine or valine. *In vitro* studies indicate that zidovudine-resistant viral isolates can become sensitive to zidovudine when they acquire the 184 mutation. The clinical relevance of such findings remains, however, not well defined.

For isolates collected in clinical studies, phenotypic resistance data showed that resistance to lamivudine monotherapy developed within 12 weeks. Evidence in isolates from antiretroviral-naive patients suggests that the combination of lamivudine and zidovudine delays the emergence of mutations conferring resistance to zidovudine. Combination therapy with lamivudine plus zidovudine did not prevent phenotypic resistance to lamivudine. However, phenotypic resistance to lamivudine did not limit the antiretroviral activity of combination therapy with lamivudine plus zidovudine. In antiretroviral therapy-naive patients, phenotypic resistance to lamivudine emerged more slowly on combination therapy than on lamivudine monotherapy. In the zidovudine-experienced patients on lamivudine plus zidovudine, no consistent pattern of changes in phenotypic resistance to lamivudine or zidovudine was observed.

Pediatrics
Pediatric subjects receiving lamivudine oral solution concomitantly with other antiretroviral oral solutions (abacavir, nevirapine/efavirenz or zidovudine) in the ARROW study developed viral resistance more frequently than those receiving tablets.

Cross-Resistance
The potential for cross-resistance between HIV reverse transcriptase inhibitors and protease inhibitors is low because of the different enzyme targets involved. Cross-resistance conferred by the M184V RT is limited within the nucleoside inhibitor class of antiretroviral agents. Zidovudine and stavudine maintain their antiretroviral activities against lamivudine-resistant HIV-1. Abacavir maintains its antiretroviral activities against lamivudine-resistant HIV-1 harbouring only the M184V mutation. The M184V RT mutant shows a < 4-fold decrease in susceptibility to didanosine and zalcitabine; the clinical significance of these findings is unknown. *In vitro* susceptibility testing has not been standardised and results may vary according

to methodological factors. HIV isolates with multidrug resistance to zidovudine, didanosine, zalcitabine, stavudine, and lamivudine were recovered from a small number of patients treated for ≥ 1 year with the combination of zidovudine and didanosine or zalcitabine. The pattern of resistant mutations in the combination therapy was different (Ala62→Val, Val75→Ile, Phe77→Leu, Phe116→Tyr and Gln151→Met) from monotherapy, with mutation 151 being most significant for multidrug resistance. Site-directed mutagenesis studies showed that these mutations could also result in resistance to zalcitabine, lamivudine, and stavudine.

Multiple-drug antiretroviral therapy containing lamivudine has been shown to be effective in antiretrovirally-naive patients as well as in patients presenting with viruses containing the M184V mutations.

The relationship between in vitro susceptibility of HIV to lamivudine and the clinical response to therapy remain under investigation.

Study EPV20001

Genotypic and phenotypic analysis of on-therapy HIV-1 isolates from patients with virologic failure (see DETAILED PHARMACOLOGY: Clinical Studies section). The data indicates that through 48 weeks, lamivudine once daily has been shown to be as effective as lamivudine twice daily, and the use of lamivudine once daily through 48 weeks does not increase the incidence or the time to emergence of resistance to lamivudine or other study drugs in the regimen. The clinical relevance of genotypic and phenotypic changes associated with lamivudine therapy has not been fully established.

Fifty-three of 554 (10%) patients enrolled in EPV20001 were identified as virological failures (plasma HIV-1 RNA level ≥ 400 copies/mL) by Week 48. Twenty-eight patients were randomized to the lamivudine once-daily treatment group and 25 to the lamivudine twice-daily treatment group. The median baseline plasma HIV-1 RNA levels of patients in the lamivudine once-daily group and lamivudine twice-daily groups were 4.9 $\log_{10}$ copies/mL and 4.6 $\log_{10}$ copies/mL, respectively.

Genotypic analysis of on-therapy isolates from 22 patients identified as virologic failures in the lamivudine once-daily group showed that isolates from 0/22 patients contained treatment-emergent mutations associated with zidovudine resistance (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E), isolates from 10/22 patients contained treatment-emergent mutations associated with efavirenz resistance (L100I, K101E, K103N, V108I, or Y181C), and isolates from 8/22 patients contained a treatment-emergent lamivudine resistance-associated mutation (M184I or M184V).

Genotypic analysis of on-therapy isolates from patients (n = 22) in the lamivudine twice-daily treatment group showed that isolates from 1/22 patients contained treatment-emergent zidovudine resistance mutations, isolates from 7/22 contained treatment-emergent efavirenz resistance mutations, and isolates from 5/22 contained treatment-emergent lamivudine resistance mutations.

Phenotypic analysis of baseline-matched on-therapy HIV-1 isolates from patients (n = 13) receiving lamivudine once daily showed that isolates from 12/13 patients were susceptible to

zidovudine; isolates from 8/13 patients exhibited a decrease in susceptibility to efavirenz, and isolates from 7/13 patients showed a decrease in susceptibility to lamivudine.

Phenotypic analysis of baseline-matched on-therapy HIV-1 isolates from patients (n = 13) receiving lamivudine twice daily showed that isolates from all 13 patients were susceptible to zidovudine; isolates from 4/13 patients exhibited a decrease in susceptibility to efavirenz, and isolates from 4/13 patients exhibited a decrease in susceptibility to lamivudine.

Cytotoxicity

The results of cytotoxicity studies in various assays have shown little cytotoxic action with lamivudine. Cytotoxicity of lamivudine was compared with that of zidovudine, zalcitabine, and didanosine in four T-lymphoblastoid cell lines; one monocyte/macrophage-like cell line; one B-lymphoblastoid cell line; and peripheral blood lymphocytes (PBLs) using both cell proliferation (CP) and [^{3}H]-thymidine uptake (Td) assays. In the CP assay, lamivudine was the least toxic of the four compounds. [^{3}H]-thymidine uptake results demonstrated a similar trend to those from the CP assays. Lamivudine had no cytotoxic effect when incubated for 10 days with phytohemagglutinin (PHA)-activated human lymphocytes or human macrophages.

The cytotoxicity of combinations of lamivudine with zidovudine, zalcitabine, or didanosine was evaluated in PHA-activated PBLs and CEM cells by measuring cellular uptake of [^{3}H]-thymidine. Lamivudine greatly reduced the cytotoxicity of zalcitabine, slightly reduced the cytotoxicity of zidovudine in some cases, and did not alter the cytotoxicity of didanosine.

In myelotoxicity studies *in vitro*, lamivudine demonstrated no toxic effects against erythroid, granulocyte-macrophage, pluripotent, or stromal progenitor cells from healthy human donors. Lamivudine was not toxic to human hematopoietic supportive stroma, nonadherent hematopoietic cells, or stromal fibroblasts and produced minimal changes in cytokine (GM-CSF) production from mitogen-stimulated bone marrow stromal cells. Lamivudine was less toxic than zidovudine, zalcitabine, ara-C, 3FT, and stavudine in these studies. In another study, lamivudine was not toxic to activated human T-cells.

TOXICOLOGY

Acute Toxicity

Acute toxicity studies have been performed in the mouse and rat. The acute oral administration of very high doses of lamivudine (two doses of 2000 mg/kg) in mice was associated with transient increases in sexual activity in males and general activity in males and females. There were no deaths and no evidence of target organ toxicity. Therefore the maximum non-lethal oral dose of lamivudine in mice is greater than two doses of 2000 mg/kg.

The acute intravenous administration of lamivudine at 2000 mg/kg was well tolerated by both mice and rats and was not associated with any target organ toxicity. A number of non-specific clinical signs were observed which were more severe in rats but were all of relatively short duration.

Long-Term Toxicity

In repeat-dose toxicity studies, lamivudine was very well tolerated in the rat at oral doses up to 2000 mg/kg b.i.d. for 6 months. Treatment-related effects were restricted to minor hematological (mainly red cell parameters), clinical chemistry and urinalysis changes, and the mucosal hyperplasia of the cecum (in the 6-month study). The no (toxicologically important) effect level was 450 mg/kg b.i.d.

In the dog, oral doses of 1500 mg/kg b.i.d. in males and 1000 mg/kg b.i.d. in females for a period of 12 months were well tolerated. Treatment-related changes included reductions in red cell counts at all dose levels associated with increased MCV and MCH, and reductions in total leucocyte, neutrophil and lymphocyte counts in high dose animals, but with no effect on bone marrow cytology. Deaths were seen in females dosed with 1500 mg/kg b.i.d. in a 3-month study but not in a 12-month study, using a dose of 1000 mg/kg b.i.d.

When administered orally for one month, at a dose of 1000 mg/kg b.i.d., lamivudine demonstrated low hematotoxic potential in the mouse, and did not significantly enhance the hematotoxicity of zidovudine or interferon α.

Carcinogenicity and Mutagenicity

Traditional 24-month carcinogenicity studies using lamivudine have been conducted in mice and rats at exposures up to 10 times (mice) and 58 times (rats) those observed in humans at recommended therapeutic doses. The following results should be noted. In mice, there appeared to be an increased incidence of histiocytic sarcoma in female mice treated with 180 mg/kg/day (6 of 60 mice) and 2000 mg/kg/day (5 of 60 mice) when compared to control mice (two control groups with 1 of 60 and 2 of 60 mice). There did not appear an increased incidence in histiocytic sarcoma in female mice treated with 600 mg/kg/day (3 of 60 mice). It should be noted that the control incidence of this type of tumour in this strain of mice can be as high as 10% similar to that found in the 180 and 2000 mg/kg/day groups. In rats, there appeared to be an increased incidence of endometrial epithelial tumours in female rats treated with 3000 mg/kg/day (5 of 55 rats) when compared to control rats (two control groups each with 2 of 55 rats). There did not appear to be an increased incidence for endometrial tumours in rats treated with 1000 mg/kg/day (2 of 55 rats) or 300 mg/kg/day (1 of 55 rats). It should be noted that there did not appear to be an increased incidences of any proliferative non-neoplastic epithelial lesions in treated female rats when compared to control rats, and the incidence of adenocarcinoma (5/55 or 9%) was only slightly higher than recorded controls at the laboratory where the study was conducted (4/50 or 8%). The statistical significance of the findings in mice and rats varied with the statistical analysis conducted, and therefore, the statistical and hence, the clinical significance of these findings are uncertain. However, based on the similarity to historical control data, it was concluded that the results of long-term carcinogenicity studies in mice and rats for lamivudine did not seem to show a carcinogenic potential relevant for humans.

Lamivudine was not active in a microbial mutagenicity screen or an *in vitro* cell transformation assay, but showed weak *in vitro* mutagenic activity in a cytogenetic assay using cultured human lymphocytes and in the mouse lymphoma assay. However, lamivudine showed no evidence of *in vivo* genotoxic activity in the rat at oral doses of up to 2,000 mg/kg (approximately 65 times the recommended human dose based on body surface area comparisons).

Reproduction and Teratology

A range of studies has been performed to assess the effects of repeated oral administration of lamivudine upon mammalian reproduction and development.

In a rat fertility study, except for a few minor changes in high dose (2000 mg/kg b.i.d) animals, the overall reproductive performance of the F_0 and F_1 generation animals, and the development of the F_1 and F_2 generation, was unaffected by treatment with lamivudine.

Lamivudine was not teratogenic in the rat or rabbit, at doses up to 2000 mg/kg b.i.d. and 500 mg/kg b.i.d., respectively. In the rabbit a slight increase in the incidence of pre-implantation loss at doses 20 mg/kg b.i.d. and above indicates a possible early embryolethal effect. There was no such effect in the rat. These marginal effects occurred at relatively low doses, which produced plasma levels comparable to those achieved in patients.

In a peri-/post-natal/juvenile toxicity study in rats, some histological inflammatory changes at the ano-rectal junction and slight diffuse epithelial hyperplasia of the caecum were observed in dams and pups at the high dose level. An increased incidence of urination upon handling was also seen in some offspring receiving 450 or 2000 mg/kg. In addition, a reduction in testes weight was observed in juvenile males at 2000 mg/kg which was associated with slight to moderate dilatation of the seminiferous tubules.

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PART III: CONSUMER INFORMATION

[Pr] Lamivudine oral solution

10 mg/mL as lamivudine

This leaflet is part III of a three-part "Product Monograph" published when lamivudine oral solution was approved for sale in Canada and is designed specifically for Consumers. Please read this leaflet carefully before you start to take your medicine. You may need to read this leaflet again during your treatment. This leaflet is a summary and will not tell you everything about lamivudine oral solution. Contact your doctor or pharmacist if you have any questions about the drug.

Lamivudine is intended for use in combination with other antiretroviral medicines. Please read the information given with these other medicines before you take lamivudine oral solution.

ABOUT THIS MEDICATION

What the medication is used for:
The Human Immunodeficiency Virus (HIV) is a retrovirus (a type of virus). Infection with HIV damages the immune system and can lead to Acquired Immune Deficiency Syndrome (AIDS) and other related illnesses.

Lamivudine oral solution belongs to a group of antiretroviral medicines called nucleoside analogue reverse transcriptase inhibitors (NRTIs), and is used in combination with other antiretrovirals to treat HIV infection.

What it does:
Lamivudine oral solution is not a cure for HIV infection or AIDS; it reduces the amount of virus in your body, and keeps it at a low level. Lamivudine oral solution also increases the CD4 cell count in your blood. CD4 cells are a type of white blood cells that are important in helping your body fight infection.

When it should not be used:
Lamivudine oral solution should not be taken if

- you previously had an allergic reaction (hypersensitivity) to the active ingredient lamivudine which is included in medicines called TRIZIVIR®, COMBIVIR® or KIVEXA®, or any other ingredients found in lamivudine oral solution. (see "What the important nonmedicinal ingredients are" sections).

What the medicinal ingredient is:
Lamivudine oral solution contains 150 mg of lamivudine in each tablespoon (15 ml).

What the important nonmedicinal ingredients are:
Lamivudine oral solution also contains artificial strawberry and banana flavours, citric acid (anhydrous), methylparaben, propylparaben, propylene glycol, sodium citrate (dihydrate), sucrose and purified water. Each 150 mg (15 mL) contains 3 g of sucrose.

What dosage forms it comes in:
Oral solution, 10 mg/mL.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Lactic acidosis (too much acid in the blood) and swollen and fatty liver (hepatomegaly with steatosis), including fatal cases, have been reported with the use of nucleoside analogues alone or in combination. If you suffer symptoms (see Serious Side Effects table), contact your doctor.
- If you also have a hepatitis B infection, you should not stop taking lamivudine oral solution without instructions from your doctor as your hepatitis may worsen/reoccur. Your doctor will monitor your condition for several months after stopping treatment with lamivudine oral solution.
- Parents or guardians should be advised to monitor pediatric patients for signs and symptoms of pancreatitis (inflammation of the pancreas; see Serious Side Effects table). If symptoms of pancreatitis occur, contact your doctor.

Before taking lamivudine oral solution, tell your doctor or pharmacist:

- About all your medicines and medical conditions, including vitamins, herbal supplements and nonprescription drugs
- If you have kidney or liver disease (including hepatitis B or C)
- If you have had previous use of any NRTI class medicine
- If you are pregnant, planning to become pregnant,

breastfeeding, or planning to breastfeed

Other Special Warnings

Remember that treatment with lamivudine oral solution does not reduce the risk of passing the infection onto others. You will still be able to pass HIV by sexual contact or by blood transfer and you should use appropriate precautions.

Some people taking medicines for HIV infection develop other conditions, which can be serious, such as reduction in blood count, pancreatitis, fatty liver, and old infections flaring up. You need to know about important signs and symptoms to look out for while you're taking lamivudine oral solution. Read the SIDE EFFECTS AND WHAT TO DO ABOUT THEM section.

It is important that your doctor know about all your symptoms even if you think they are not related to HIV infection. Your doctor may need to change the dose of your medicine.

If you are a diabetic, please note that 150 mg (15 mL) of lamivudine oral solution contains 3 g of sugar.

Due to the sugar content of lamivudine oral solution, you should clean your teeth regularly to reduce the risk of tooth decay.

Patients with HIV-1/HCV (hepatitis C) co-infection should be informed that hepatic decompensation (a severe liver problem – sometimes fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin. If you suffer liver symptoms such as nausea, fatigue, abdominal pain, jaundice (yellowing of the eyes or skin) or lack of appetite, contact your doctor immediately.

Your blood sugar levels (glucose) or levels of fats (lipids) in your blood may increase with HIV treatment. Your doctor may order blood tests for you.

Use Of This Medicine During Pregnancy And Breastfeeding

If you are pregnant, or planning to become pregnant soon, you must inform your doctor before taking any medicine. The safe use of lamivudine in pregnancy has not been established. Your doctor will decide whether you should continue to be treated with lamivudine oral solution if you are pregnant. If you take lamivudine oral solution while you are pregnant, talk to your doctor about how you can be included in the Antiretroviral Pregnancy Registry.

Babies and infants exposed to Nucleoside Reverse Transcriptase Inhibitors (NRTIs) during pregnancy or labour show minor temporary increases in blood levels of lactate. The clinical importance of these temporary increases is unknown.

These findings do not affect current recommendations to use antiretroviral therapy in pregnant women to prevent transmission of HIV to their babies. There have been very rare reports of disease that affect the neonatal (babies) nervous system such as delayed development and seizures. The long term effects of lamivudine are not known.

It is recommended that HIV-infected women do not breastfeed their infants in order to avoid transmission of HIV from mother to child. The active substance in lamivudine oral solution is found in human breast milk.

You are recommended not to breastfeed your baby while taking lamivudine oral solution.

<u>Remember</u>: this medicine is for you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.

INTERACTIONS WITH THIS MEDICATION

It is important that your doctor knows about all your medicines so that you get the best possible treatment. Tell your doctor about all your medicines, including vitamin supplements, herbal remedies or homeopathic remedies, including those you have bought yourself.

Lamivudine oral solution should not be taken with emtricitabine.

Some medicines may affect how lamivudine works, or make it more likely that you'll have side effects. These medicines include:

- sorbitol-containing medicines (usually liquids) used regularly.
- trimethoprim-sulphamethoxazole (also known as co-trimoxazole; an antibiotic used to treat *Pneumocystis jiroveci* pneumonia (often referred to as PCP) or toxoplasmosis).

PROPER USE OF THIS MEDICATION

<u>Usual dose:</u>

Take lamivudine oral solution **exactly as your doctor has advised you, and try not to miss any doses.** If you are

unsure about how to take it, ask your doctor or pharmacist.

Lamivudine oral solution can be taken with or without food.

Adults, Adolescents and Children (weighing at least 25 kg): One tablespoonful (15 mL) of oral solution, two times a day. For once-a-day dosing: take two tablespoonfuls (30 mL) of oral solution once a day.

Dosing Schedule	Solution
Once a day	Two tablespoons = 30 mL of solution
Twice a day	One tablespoon = 15 mL of solution

If you have a kidney problem, your dose may be altered. Please follow the instructions of your doctor.

Children (aged 3 months and older and weighing less than 25 kg): if you are giving lamivudine oral solution to a child, carefully follow the instructions of your doctor.

The recommended oral dose of lamivudine oral solution for children 3 months of age and older and weighing less than 25 kg is 4 mg/kg twice daily (up to a maximum of 15 mL twice daily) or 8 mg/kg once daily (up to a maximum of 30 mL once daily).

Overdose:

If you think you have taken too much lamivudine oral solution, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
It is important to take this medicine as prescribed to ensure you get maximum benefit. If you forget to take a dose, take it as soon as you remember, and then continue as before. Do not double dose to make up for forgotten individual doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, lamivudine oral solution can have side effects. For this reason it is very important that you inform your doctor about any changes in your health.

Consult your doctor **at your next visit** if any of the following undesirable events occur:

- Headaches, nausea, vomiting, upper abdominal pain, diarrhea, fever, rash, fatigue, a general feeling of being unwell, or a numbness, tingling sensation or sensation of weakness in your limbs.

Lamivudine oral solution may also cause a decrease in certain types of blood counts (including red blood cells, white blood cells and platelets) and increase in certain liver enzymes.

Changes in your immune system (Immune Reconstitution Inflammatory Syndrome) can happen when you start taking HIV medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time, or you could develop an autoimmune disease in which your immune system reacts against your own body (e.g. Grave's disease (which affects the thyroid gland), Guillain-Barre syndrome (which affects the nervous system) or polymyositis (which affects the muscles) and it may develop at any time, sometimes months later after the start of HIV therapy). Sometimes symptoms can be severe, so if you develop high temperature (fever), joint or muscle pain, redness, rash, swelling, or fatigue or any new symptoms contact your doctor straight away.

Always tell your doctor or pharmacist about any undesirable effects, even those not mentioned in this leaflet. If you feel unwell in any other way that you do not understand, tell your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
		Only if severe	**In all cases**	
Rare	Allergic reactions and symptoms such as swelling of eyes, face, lips, throat, sudden wheeziness, chest pain and tightening, skin rash or hives anywhere on the body.			√
	Lactic acidosis (high level of lactic acid in the blood) and symptoms such as			

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
weight loss, fatigue, malaise, nausea, vomiting, abdominal pain, and shortness of breath.			√
Swollen and fatty liver (severe hepatomegaly with steatosis) and symptoms such as nausea, vomiting, abdominal pain, weakness and diarrhea.			√
Blood problems and symptoms such as anemia (lowered red blood cell count) resulting in fatigue, breathlessness, and low white blood cell count making you more prone to infections.		√	
Pancreatitis (inflammation of the pancreas) and symptoms such as severe stomach cramps, nausea, vomiting.			√

HOW TO STORE IT

Lamivudine oral solution should be stored between 15 - 25°C.

As with all medicines, keep lamivudine oral solution out of the reach and sight of children.

Do not take your medicine after the expiry date shown on the bottle and/or the carton.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This leaflet does not tell you everything about your medicine. If you have any questions or are not sure about anything, then ask your doctor or pharmacist. You may need to read this leaflet again. Please do not throw it away until you are no longer taking lamivudine oral solution.

If you want more information about Lamivudine oral solution:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website www.auropharma.ca, or by calling 1-855-648-6681.

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