PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrAPO-LAMIVUDINE

Lamivudine (as lamivudine methanol solvate) Tablets

Tablets, 150 mg and 300 mg, Oral

Apotex Standard

Antiretroviral Agent

APOTEX INC.
150 Signet Drive
Toronto, Ontario
M9L 1T9

Date of Initial Authorization:
APR 27, 2012

Date of Revision:
JUN 2, 2023

Submission Control Number: 271187

RECENT MAJOR LABEL CHANGES

3 SERIOUS WARNINGS AND PRECAUTIONS BOX	06/2023
4 DOSAGE AND ADMINISTRATION, 4.1 Dosing Considerations	[Removed] 06/2023
4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment	06/2023
7 WARNINGS AND PRECAUTIONS	06/2023
7 WARNINGS AND PRECAUTIONS, General	[Removed] 06/2023

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

APO-LAMIVUDINE (lamivudine) in combination with other antiretroviral agents is indicated for the treatment of HIV infection.

1.1 Pediatrics

Pediatrics (< 18 years of age): APO-LAMIVUDINE is indicated in pediatric patients weighing greater than or equal to 14 kg in combination with other antiretroviral agents.

- Before prescribing APO-LAMIVUDINE tablets, children should be assessed for the ability to swallow tablets. If a child is unable to reliably swallow APO-LAMIVUDINE tablets, the oral solution formulation should not be prescribed.

1.2 Geriatrics

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.

2 CONTRAINDICATIONS

APO-LAMIVUDINE is contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of the products (see section 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **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 APO-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, APO-LAMIVUDINE should be used with caution. Treatment with APO-LAMIVUDINE should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur (see section 8 ADVERSE REACTIONS).

- **Important Differences among Lamivudine-Containing Products**
  Lamivudine tablets used to treat HIV-1 infection contain a higher dose of the active ingredient (lamivudine) than lamivudine tablets and oral solution used to treat chronic HBV infection. Patients with HIV-1 infection should receive only dosage forms appropriate for treatment of HIV-1.

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

APO-LAMIVUDINE can be taken with or without food.

Adults, Adolescents and Children weighing at least 25 kg 271197

The recommended oral dose of APO-LAMIVUDINE 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 **7 WARNINGS AND PRECAUTIONS**, **10 CLINICAL PHARMACOLOGY** and **14 CLINICAL TRIALS**).

Scored Tablets

APO-LAMIVUDINE is also available as a scored tablet for HIV-1-infected pediatric patients weighing greater than or equal to 14 kg for whom a solid dosage form is appropriate. Before prescribing APO-LAMIVUDINE Tablets, children should be assessed for the ability to swallow tablets. If a child is unable to reliably swallow APO-LAMIVUDINE Tablets, the oral solution formulation should be prescribed. The recommended oral dosage of APO-LAMIVUDINE Tablets for HIV-1-infected pediatric patients is presented in Table 1.

Table 1 - Dosing Recommendations for APO-LAMIVUDINE Scored (150 mg) Tablets in Pediatric Patients

Weight (kg)	Once-Daily Dosing Regimen	Twice-Daily Dosing		Total Daily Dose
		AM Dose	PM Dose	
14 to <20	1 tablet (150 mg)	½ tablet (75 mg)	½ tablet (75 mg)	150 mg
≥20 to <25	1 ½ tablets (225 mg)	½ tablet (75 mg)	1 tablet (150 mg)	225 mg
≥25	2 tablets (300 mg)	1 tablet (150 mg)	1 tablet (150 mg)	300 mg

Pediatric patients weighing less than 14 kg

APO-LAMIVUDINE is not recommended for pediatric patients weighing less than 14 kg because appropriate dose adjustment is not possible in these patients.

Hepatic Impairment

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

Renal Impairment

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 APO-LAMIVUDINE should be adjusted, as shown in Table 2 in accordance with creatinine clearance.

APO-LAMIVUDINE is not recommended in adult and pediatric patients weighing equal or greater than 25 kg with creatinine clearance less than 30 mL/min because appropriate dose adjustment is not possible in these patients.

APO-LAMIVUDINE is not recommended in pediatric patients with renal impairment weighing less than 25 kg because appropriate dose adjustment is not possible in these patients.

Table 2 - Adjustment of Dosage of APO-LAMIVUDINE in Accordance with Creatinine Clearance in Adults, Adolescents and Children weighing ≥25 kg

Creatinine clearance (mL/min)	Recommended Dosage of APO-LAMIVUDINE
≥ 50	150 mg twice daily or 300 mg once daily
30 to 50	150 mg once daily
15 to 29	150 mg first dose, then 100 mg once daily
5 to 14	150 mg first dose, then 50 mg once daily
< 5	50 mg first dose, then 25 mg once daily

4.5 Missed Dose

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

5 OVERDOSAGE

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.

No specific signs or symptoms have been identified following acute overdose with lamivudine, apart from those listed as adverse reactions.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Oral	Tablets / 150 mg and 300 mg	Colloidal silicon dioxide, crospovidone, ferric-ferrous oxide (300 mg tablet), hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose anhydrous, magnesium stearate, polyethylene glycol and titanium dioxide.

APO-LAMIVUDINE 150 mg Tablets: Each white to off-white, diamond shaped, biconvex film-coated tablet contains 150 mg of lamivudine. Engraved “APO” on one side, “LMV” score “150” on the other side. Available in bottles of 100 and 60 tablets.

APO-LAMIVUDINE 300 mg Tablets: Each grey, diamond shaped, biconvex film-coated tablet contains 300 mg of lamivudine. Engraved “APO” on one side, “LMV 300” on the other side. Available in bottles of 100 and 30 tablets.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX at the beginning of Part I: Health Professional Information.

General

APO-LAMIVUDINE (lamivudine) should not be administered concomitantly with other products containing lamivudine including lamivudine tablets and oral solution, lamivudine and zidovudine tablets, abacavir and lamivudine tablets, dolutegravir, abacavir, and lamivudine tablets, or dolutegravir and lamivudine tablets.

APO-LAMIVUDINE should also not be administered concomitantly with emtricitabine containing products, including efavirenz/emtricitabine/tenofovir disoproxil fumarate tablets, emtricitabine capsules, emtricitabine/tenofovir disoproxil fumarate tablets, emtricitabine/rilpivirine/ tenofovir disoproxil fumarate tablets, elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate tablets, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide tablets,

emtricitabine/tenofovir alafenamide tablets, bictegravir/emtricitabine/tenofovir alafenamide tablets, darunavir/cobicistat/emtricitabine/tenofovir alafenamide tablets, or emtricitabine/ rilpivirine/tenofovir alafenamide tablets.

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

Patients receiving APO-LAMIVUDINE 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.

Endocrine and Metabolism

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.

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. Female sex and obesity may be risk factors.

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

Patients Co-infected with Hepatitis B virus

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

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 lamivudine 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

Immune reconstitution inflammatory syndrome (IRIS) has been reported in HIV-infected patients treated with combination antiretroviral therapy, including lamivudine. During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections [such as *Mycobacterium avium-complex* (MAC), cytomegalovirus (CMV), *Pneumocystis jirovecii pneumonia* (PCP), and *tuberculosis* (TB)], which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, autoimmune hepatitis 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 Impairment

Patients with impaired renal function may be at a greater risk of toxicity from APO-LAMIVUDINE due to decreased renal clearance of the drug. Consideration should be given to appropriate reduction in the dose of lamivudine (see **4.2 Recommended Dose and Dosage Adjustment**).

7.1 Special Populations

7.1.1 Pregnant Women

Lamivudine has not been studied in pregnant women. Therefore, APO-LAMIVUDINE should not be used in pregnant women unless the potential benefits to the mother outweigh the potential risk to the fetus (see **10 CLINICAL 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 **16 NON-CLINICAL 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 APO-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 and also to register patients by calling Apotex Drug Safety at 1-800-667-4708.

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.

7.1.2 Breast-feeding

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 APO-LAMIVUDINE**.

7.1.3 Pediatrics

The safety and effectiveness of lamivudine tablets have been established in pediatric patients weighing greater than or equal to 14 kg. Use of lamivudine is supported by pharmacokinetic trials and evidence from adequate and well-controlled trials of lamivudine in adults and pediatric subjects (see **4.2 Recommended Dose and Dosage Adjustment**, **10.3 Pharmacokinetics, Special Populations and Conditions, Pediatrics**, **14.1 Clinical Trials by Indication, Table 13** and **14.1 Clinical Trials by Indication, Study Results, Clinical Endpoint Study in Pediatric Patients**).

7.1.4 Geriatrics

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 APO-LAMIVUDINE in elderly patients, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The following adverse reactions are discussed in the **3 SERIOUS WARNINGS AND PRECAUTIONS BOX** and **7 WARNINGS AND PRECAUTIONS** sections:

- Lactic acidosis and severe hepatomegaly (see **7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**)
- Post-treatment exacerbations of hepatitis B (see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX**)
- Serum lipids and blood glucose (see **7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism**)
- Pancreatitis (see **7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic** **and** **3 SERIOUS WARNINGS AND PRECAUTIONS BOX - Pancreatitis in Pediatric Patients**)

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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 4 and Table 5. 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 6.

Table 4 - 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 5 - 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%

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)
Hypotension	0%	<1%

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

Table 6 - 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%

Adverse Event	Lamivudine 150 mg b.i.d. plus Zidovudine (n = 251)	Zidovudine (n = 230)
Skin & appendages		
Skin rashes	9%	6%
Musculoskeletal		
Musculoskeletal pain	12%	10%
Myalgia	8%	6%
Arthralgia	5%	5%

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

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 7.

Table 7 - 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		

Adverse Event	Lamivudine plus Zidovudine (n = 236)	Didanosine (n = 235)
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.

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.

8.3 Less Common Clinical Trial Adverse Reactions

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%).

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

The frequencies of selected laboratory abnormalities (Grades 3 and 4) in adults during therapy are listed in Table 8.

Table 8 - 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<8.0 g/dL)	3%	2%	2%	3%	<1%	<1%

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.♠
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

Selected laboratory abnormalities experienced by patients without or minimal (≤ 56 days) prior antiretroviral therapy are listed in Table 9.

Table 9: 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 g/dL)	4%	2%
Thrombocytopenia (platelets < 50,000/mm^3)	1%	3%

Test (Abnormal Level)	Lamivudine plus Zidovudine	Didanosine
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.

8.5 Post-Market Adverse 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 **7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**)

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 **7 WARNINGS AND PRECAUTIONS, Immune**)

Musculoskeletal: arthralgia, muscle disorders including very rarely rhabdomyolysis

Nervous: headache, paresthesia, peripheral neuropathy

Other: alopecia

Skin: pruritus, rash, urticaria

9 DRUG INTERACTIONS

9.2 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 P-glycoprotein (Pgp), multidrug and toxin extrusion protein 1 (MATE1), MATE2-K or organic cation transporter 3 (OCT3). Lamivudine is therefore not expected to affect the plasma concentrations of drugs that are substrates of these drug transporters.

Lamivudine is an inhibitor of OCT1 and OCT2 *in vitro* with IC50 values of 17 and 33 mcM, respectively, however lamivudine has low potential to affect the plasma concentrations of OCT1 and OCT2 substrates at therapeutic drug exposures (up to 300 mg).

Effect of other agents on the pharmacokinetics of lamivudine

Lamivudine is a substrate of MATE1, MATE2-K and OCT2 *in vitro*. Trimethoprim (an inhibitor of these drug transporters) has been shown to increase lamivudine plasma concentrations, however this interaction is not considered clinically significant as no dose adjustment of lamivudine is needed.

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

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

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 10 - 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 7 WARNINGS AND PRECAUTIONS, General).
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 and 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	A modest increase in C_{max} (28%) was

Proper name	Effect	Clinical comment
	pharmacokinetics of lamivudine (see 10 CLINICAL PHARMACOLOGY section)	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.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 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.

10.3 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 mcg/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 **10.3 Pharmacokinetics, Special Populations and Conditions, Pediatrics**).

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.

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 mcg/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 86% ± 16% (mean ± S.D.) for the 150 mg tablet.

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 was pharmacokinetically equivalent to lamivudine 150 mg twice daily with respect to plasma $AUC_{24,SS}$. Intracellular lamivudine triphosphate concentrations in peripheral blood mononuclear cells were also pharmacokinetically equivalent with respect to $AUC_{24,SS}$ and $C_{max24,SS}$.

Lamivudine tablets were 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 tablets 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 mcg /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 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 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.

The plasma lamivudine half-life after oral dosing is 18 to 19 h and the active moiety, intracellular lamivudine triphosphate, has a prolonged terminal half-life in the cell (16 to 19 h).

Special Populations and Conditions

Pediatrics: The pharmacokinetics of lamivudine have been studied after either single or repeat doses of lamivudine in 210 pediatric subjects. Pediatric subjects receiving lamivudine oral tablets according to the recommended dosage regimen achieved plasma concentrations of lamivudine similar to adults. The absolute bioavailability of lamivudine tablets are lower in children than adults.

The pharmacokinetics of lamivudine dosed once daily in HIV-1-infected pediatric patients aged 3 to 12 years was evaluated in a study (ARROW PK [n=35]). This study was designed as 2 – period, crossover, open-label pharmacokinetic studies of twice-versus once-daily dosing of abacavir and lamivudine. This study demonstrated that once-daily dosing provides equivalent

AUC_{0-24} to twice-daily dosing of lamivudine at the same total daily dose. The mean C_{max} was approximately 80% higher with lamivudine once-daily dosing compared with twice-daily dosing.

Table 11: Pharmacokinetic Parameters (Geometric Mean [95% CI]) after Repeat Dosing of Lamivudine in a Pediatric Trial

	Trial (Number of Subjects)	
	ARROW PK (n = 35)	
Age Range	**3-12 years**	
Formulation	**Tablet**	
Parameter	**Once Daily**	**Twice Daily**
C_{max} (mcg/mL)	**3.17 (2.76, 3.64)**	**1.80 (1.59, 2.04)**
$AUC_{(0-24)}$ (mcg·h/mL)	**13.0 (11.4, 14.9)**	**12.0 (10.7, 13.4)**

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.

Pregnancy and Breast-feeding: Following oral administration, lamivudine pharmacokinetics in late pregnancy were similar to non-pregnant adults.

Renal Insufficiency: The pharmacokinetic properties of lamivudine were determined in a small group of HIV-infected adults with impaired renal function, and are summarized in Table 12.

Table 12 - 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} (mcg/mL)	2.6 ± 0.5	3.6 ± 0.8	5.8 ± 1.2
AUC_{∞} (mcg·h/mL)	11 ± 1.7	48 ± 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 **4.2 Recommended Dose and Dosage Adjustment**).

11 STORAGE, STABILITY AND DISPOSAL

Store at controlled room temperature (15°C to 30°C). Protect from moisture.

Keep out of reach and sight of children.

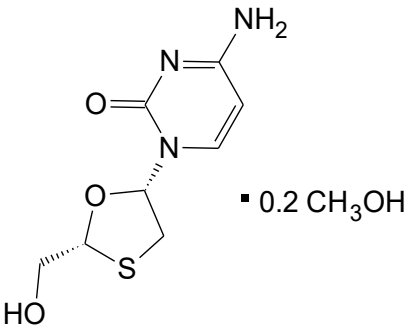
12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name:	Lamivudine (as lamivudine methanol solvate)
Chemical Name:	4-amino-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]pyrimidin-2(1*H*)-one methanol solvate (2*R*-*cis*)- 4-amino-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-2(1*H*)-pyrimidinone methanol solvate(–)-1-[(2*R*,5*S*)-2-(hydroxymethyl-1,3-oxathiolan-5-yl]cytosine
Molecular formula and molecular mass:	$C_8H_{11}N_3O_3S \cdot 0.2\ CH_3OH$; 235.66 g/mol
Structural Formula:	
Description:	Lamivudine methanol solvate is white to off-white powder.
Physicochemical properties:	Lamivudine methanol solvate has a melting range of 177° to 178°C and is highly soluble in water. The pKa of the protonated lamivudine was found to be 4.3. The pH of the 1% solution of solvent-free form is 6.9.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

APO-LAMIVUDINE (lamivudine) in combination with other antiretroviral agents for the treatment of HIV infection

Trial Design and Study Demographics

Table 13 - Summary of patient demographics for clinical trials for the treatment of HIV infection

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age	Sex (% male)
Clinical Endpoint Study in Adults **NUCB3007 (CAESAR)**	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.	Dosage: Eligible subjects were randomised to 1 of the following 3 study regimens for a period of 52 weeks: • Current treatment + placebo lamivudine twice daily (BID) + placebo LOV 3 times daily (TID) • Current treatment + lamivudine 150 mg BID + placebo LOV TID • Current treatment + lamivudine 150 mg BID + LOV 100 mg TID Route of administration: Oral. Study duration: The median duration on study was 12 months.	A total of 1816 HIV-infected adults with 25 to 250 CD4 cells/mm^3 (median = 122 cells/mm^3) at baseline were enrolled. 84% were nucleoside-experienced, and 16% were therapy-naive.	36 years	87%
Surrogate Endpoint Study in Therapy-Naive Adults **EPV20001**	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	Dosage: 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 Route of administration: Oral.	A total of 554 antiretroviral treatment-naive HIV-infected adults enrolled: Caucasian (50%), baseline CD4 cell counts of 69 to 1089	35 years	79%

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age	Sex (% male)
	600 mg once daily.	Study duration: 48 Weeks.	cells/mm^3 (median = 362 cells/mm^3), and median baseline plasma HIV RNA of 4.66 log10 copies/mL.		
Clinical Endpoint Study in Pediatric Patients **ACTG300**	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 mean baseline CD4 cell count was 868 cells/mm^3 (mean: 1060 cells/mm^3 and range: 0 to 4650 cells/mm^3 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.	Dosage: not available Route of administration: Oral. Duration: 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	471 symptomatic, HIV-infected pediatric patients, without, or with, minimal (≤56 days) prior antiretroviral therapy 58% were female, and 86% were non-Caucasian	2.7 years (range 6 weeks to 14 years)	42%
Once-Daily Dosing **ARROW (COL105677)**	A 5-year randomized, multicenter trial which evaluated multiple aspects of clinical management of HIV-1	Dosage: not available Route of administration: Oral. Duration: After 36 weeks	Of the 1206 original subjects enrolled in the study, 669	Range: 3 months to 17 years	Not available

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age	Sex (% male)
	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.	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.	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.		

14.2 Study Results

Clinical Endpoint Study in Adults

Results are summarized in Table 14.

Table 14 - 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%)

Endpoint		Current Therapy (n = 460)	Lamivudine plus Current Therapy (n = 896)	Lamivudine plus a NNRTI* plus Current Therapy (n = 460)
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

Percentages of patients with HIV RNA < 400 copies/mL and outcomes of treatment through are summarized in Table 15.

Table 15 - 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

Results are summarized in Table 16.

Table 16 - 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

The proportion of subjects with HIV-1 RNA of less than 80 copies per mL through 96 weeks is shown in Table 17. The differences between virologic responses in the two treatment arms were comparable across baseline characteristics for gender and age.

Table 17 - 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 (%)

	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 (<200 c/mL, <400 c/mL, <1000 c/mL). Virologic outcomes between treatment arms were comparable across baseline characteristics (gender, age, or viral load at randomization).

14.3 Comparative Bioavailability Studies

A randomized, two-way crossover comparative bioavailability study of APO-LAMIVUDINE Tablets, 300 mg (APOTEX INC.) and EPIVIR® Tablets, 300 mg (GlaxoSmithKline, USA) was conducted in 24 healthy adult male subjects under fasting conditions. The results from measured data are summarized in the following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Lamivudine (1 x 300 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	13071.0 13312.2 (20)	13582.5 13813.0 (19)	96.2	90.5 - 102.3
AUC_I (ng·h/mL)	13327.9 13566.3 (20)	13829.1 14060.2 (19)	96.4	90.8 – 102.3
C_{max} (ng/mL)	2990.4 3093.4 (25)	3074.9 3152.0 (23)	97.3	87.7 – 107.9
T_{max}[3] (h)	0.75 (0.5 – 2.0)	0.75 (0.5 – 3.0)		
T_{half}[4] (h)	7.47 (15)	7.41 (12)		

[1] APO-LAMIVUDINE (as lamivudine methanol solvate) Tablets, 300 mg (APOTEX INC.)
[2] EPIVIR® (lamivudine) Tablets, 300 mg (GlaxoSmithKline, USA, purchased in the USA).
[3] Expressed as median (range) only.
[4] Expressed as arithmetic mean (CV %) only.

15 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.

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 standardized 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 14 CLINICAL TRIALS). 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.

16 NON-CLINICAL TOXICOLOGY

General 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: 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).

Reproductive and Developmental Toxicology: 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.

17 SUPPORTING PRODUCT MONOGRAPHS

1. Pr3TC Tablets, 150 mg and 300 mg, oral solution, 10 mg/mL, submission control 270742, Product Monograph, ViiV Healthcare ULC (MAY 3, 2023)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]APO-LAMIVUDINE

Lamivudine Tablets

Read this carefully before you start taking **APO-LAMIVUDINE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **APO-LAMIVUDINE**.

Serious Warnings and Precautions

- **Worsening of hepatitis B:** If you also have a hepatitis B infection, your hepatitis may become worse after stopping treatment with APO-LAMIVUDINE. Your healthcare professional will monitor your condition for several months after stopping treatment with APO-LAMIVUDINE.
- **Pancreatitis in children and adolescents:** Children and adolescents should be monitored for signs and symptoms of pancreatitis (inflammation of the pancreas; see Serious Side Effects table). If symptoms of pancreatitis occur, children and adolescents should get immediate medical help.

What is APO-LAMIVUDINE used for?

APO-LAMIVUDINE is used to treat Human Immunodeficiency Virus (HIV) infection in:

- Adults
- Children (weighing greater than or equal to 14 kg) and adolescents.

It is used along with other medicines used to treat HIV.

How does APO-LAMIVUDINE work?

APO-LAMIVUDINE is a type of medicine known as an antiretroviral. APO-LAMIVUDINE is not a cure for HIV infections or AIDS; it reduces the amount of virus in your body and keeps it at a low level. APO-LAMIVUDINE maintains or 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.

What are the ingredient in APO-LAMIVUDINE?

Medicinal Ingredients: Lamivudine

Nonmedicinal ingredients (150 mg): colloidal silicon dioxide, crospovidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose anhydrous, magnesium stearate, polyethylene glycol and titanium dioxide.

Nonmedicinal ingredients (300 mg): colloidal silicon dioxide, crospovidone, ferric-ferrous oxide, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose anhydrous, magnesium stearate, polyethylene glycol and titanium dioxide

APO-LAMIVUDINE comes in the following dosage forms:

150 mg and 300 mg tablets.

Do not use APO-LAMIVUDINE if:

- you are allergic to lamivudine or to any of the other ingredients in APO-LAMIVUDINE

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APO-LAMIVUDINE. Talk about any health conditions or problems you may have, including if you:

- have kidney problems
- have liver problems (including hepatitis B or C)
- have had previous use of any NRTI class medicine
- are obese

Other warnings you should know about:

Lactic acidosis and liver problems: APO-LAMIVUDINE can cause a serious condition called lactic acidosis together with hepatomegaly (swollen and enlarged liver). Lactic acidosis is where you have too much lactic acid in your blood. Symptoms include weakness, loss of appetite, sudden unexplained weight loss, upset stomach and difficulty breathing or rapid breathing. Talk to a healthcare professional right away if you get any symptoms of lactic acidosis. Lactic acidosis occurs more often in women and in obese people. If you have liver problems you may also be more at risk of getting this condition. While you are being treated with APO-LAMIVUDINE your healthcare professional will monitor you closely for signs of lactic acidosis.

Blood tests: Your blood sugar levels (glucose) or levels of fats (lipids) in your blood may increase with HIV treatment. Your liver enzyme values might change too. Your doctor may order blood tests for you and will interpret the results.

Resistant hepatitis B infection: If you are also infected with hepatitis B virus, the virus can change during your treatment with APO-LAMIVUDINE. This might make it harder to treat (resistant). If this happens, your hepatitis might get worse.

Pregnancy and birth defects: Tell your doctor if you are pregnant, think you might be pregnant or are planning to become pregnant. You should not take APO-LAMIVUDINE while you are pregnant unless your healthcare professional tells you to. This is because APO-LAMIVUDINE can harm an unborn baby.

Pregnancy registry: There is a pregnancy registry for women who take antiretroviral medicines while they are pregnant. The purpose of this registry is to collect information about the health of you and your baby. If you do become pregnant while taking APO-LAMIVUDINE, talk to your healthcare professional about taking part in this registry.

Breastfeeding: Do not breastfeed while taking APO-LAMIVUDINE. Women who are HIV positive should not breastfeed because HIV infection can be passed to the baby through breast milk. APO-LAMIVUDINE can also pass into breast milk and harm your baby. Talk to your healthcare professional about how to feed your infant.

Immune System Changes: Changes to your immune system (Immune Reconstitution Inflammatory Syndrome) can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time.

Autoimmune disorders (when the immune system attacks health body tissue), may also occur after you start taking medicines for HIV infection. Examples of this include: Grave's disease (which affects the thyroid gland), Guillain-Barré syndrome (which affects the nervous system), polymyositis (which affects the muscles), or autoimmune hepatitis (which affects the liver). Autoimmune disorders may occur many months after the start of treatment.
Look for any symptoms such as:

- high temperature (fever), redness, rash or swelling
- fatigue
- joint or muscle pain
- numbness or weakness beginning in the hands and feet and moving up towards the trunk of the body
- palpitations (chest pain) or rapid heart rate

If you notice these or any other symptoms of inflammation or infection, tell your healthcare professional immediately.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

APO-LAMIVUDINE should not be used:

- with other products containing lamivudine including lamivudine tablets and oral solution, lamivudine and zidovudine tablets, abacavir and lamivudine tablets, dolutegravir, abacavir, and lamivudine tablets, or dolutegravir and lamivudine tablets because it may interact with APO-LAMIVUDINE.
- with products containing emtricitabine, including efavirenz/emtricitabine/tenofovir disoproxil fumarate tablets, emtricitabine capsules, emtricitabine/tenofovir disoproxil fumarate tablets, emtricitabine/rilpivirine/tenofovir disoproxil fumarate tablets, elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate tablets,

elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide tablets, emtricitabine/tenofovir alafenamide tablets, bictegravir/emtricitabine/tenofovir alafenamide tablets, darunavir/cobicistat/emtricitabine/tenofovir alafenamide tablets or emtricitabine/rilpivirine/tenofovir alafenamide tablets because it may interact with APO-LAMIVUDINE.

The following may interact with APO-LAMIVUDINE:

- medicines containing sorbitol, these are usually liquids.
- trimethoprim-sulphamethoxazole (also known as co-trimoxazole), an antibiotic used to treat pneumonia.

How to take APO-LAMIVUDINE:

- Always take APO-LAMIVUDINE exactly as your healthcare professional has told you to.
- Check with your healthcare professional if you are not sure.
- You can take APO-LAMIVUDINE with or without food.
- Swallow APO-LAMIVUDINE tablets whole with water.

Usual Dose

Adults, Adolescents and Children (weighing at least 25 kg): Twice-a-day dosing: swallow one tablet (150 mg) two times a day.

For once-a-day dosing: swallow one tablet (300 mg) once a day.

Dosing Schedule	**Tablets**
Once a day	One 300 mg tablet
Twice a day	One 150 mg tablet

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

Children (weighing 14 kg to less than 25 kg): if you are giving APO-LAMIVUDINE to a child, carefully follow the instructions of your healthcare professional.

<u>Tablets:</u>

For children able to swallow tablets as determined by the healthcare professional/parent:

Children weighing 14 kg to less than 20 kg: one-half of a scored APO-LAMIVUDINE tablet twice daily or one tablet taken once daily.

Children weighing at least 20 kg and less than 25 kg: one-half of a scored APO-LAMIVUDINE tablet taken in the morning and one whole tablet taken in the evening or one and a half tablets taken once daily.

Overdose:

If you think you, or a person you are caring for, have taken too much APO-LAMIVUDINE, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take a dose, take it as soon as you remember. Then continue as before. Do not take a double dose to make up for a forgotten dose.

What are possible side effects from using APO-LAMIVUDINE?

These are not all the possible side effects you may have when taking APO-LAMIVUDINE. If you experience any side effects not listed here, tell your healthcare professional.

Side effects include:

- headaches
- nausea
- vomiting
- upper abdominal pain
- diarrhea
- fever
- rash
- hair loss or thinning of hair
- fatigue
- a general feeling of being unwell
- numbness
- tingling sensation or sensation of weakness in your limbs

Serious side effects 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**	

Serious side effects 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: 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): weight loss, fatigue, malaise, nausea, vomiting, abdominal pain, and shortness of breath.			✓
Severe hepatomegaly with steatosis (swollen and fatty liver): nausea, vomiting, abdominal pain, weakness and diarrhea.			✓
Anemia (decrease in red blood cell count): fatigue, breathlessness, weakness.		✓	
Thrombocytopenia (Reduction in the number of platelets. Platelets are cells that make the blood clot): more likely to bruise (due to reduction of platelets).		✓	
Neutropenia (low white blood cell count): fatigue, fever, infections.		✓	
Breakdown of muscle tissue: muscle tenderness or pain, and weakness.		✓	
Pancreatitis (inflammation of the pancreas): abdominal pain, nausea, vomiting.			✓
FREQUENCY NOT KNOWN			
Immune System Changes (Immune Reconstitution Inflammatory Syndrome and Autoimmune Disorders): fever, redness, rash or swelling, fatigue, joint or muscle pain, numbness or weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, chest pain, rapid heart rate.		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad

enough to interfere with your daily activities, tell your healthcare professional.

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/adverse-reaction-reporting.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.

Storage:

Store APO-LAMIVUDINE tablets at room temperature (15°C to 30°C). Protect from moisture.

Keep out of reach and sight of children.

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

If you want more information about APO-LAMIVUDINE:

- 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://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (http://www.apotex.ca/products), or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

Last Revised: JUN 2, 2023