

PRODUCT MONOGRAPH

Pr3TC[®]

lamivudine

150 mg tablets, 300 mg tablets, and 10 mg/mL oral solution

Antiretroviral Agent

ViiV Healthcare Shire Canada
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Mississauga, Ontario
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Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION.....3
SUMMARY PRODUCT INFORMATION3
INDICATIONS AND CLINICAL USE.....3
CONTRAINDICATIONS4
WARNINGS AND PRECAUTIONS.....4
ADVERSE REACTIONS.....8
DRUG INTERACTIONS16
DOSAGE AND ADMINISTRATION17
OVERDOSAGE18
ACTION AND CLINICAL PHARMACOLOGY19
STORAGE AND STABILITY20
SPECIAL HANDLING INSTRUCTIONS20
DOSAGE FORMS, COMPOSITION AND PACKAGING20

PART II: SCIENTIFIC INFORMATION22
PHARMACEUTICAL INFORMATION.....22
CLINICAL TRIALS.....23
DETAILED PHARMACOLOGY25
MICROBIOLOGY28
TOXICOLOGY31
REFERENCES.....34

PART III: CONSUMER INFORMATION.....38

Pr3TC®

lamivudine

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablets/ 150 mg	hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate and titanium dioxide
	Tablets/ 300 mg	black iron oxide, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate and titanium dioxide
	Oral Solution/ 10 mg/mL	artificial strawberry and banana flavours, citric acid (anhydrous), hydrochloric acid, methylparaben, propylparaben, propylene glycol, sodium citrate (dihydrate), sodium hydroxide, sucrose and water

INDICATIONS AND CLINICAL USE

3TC® (lamivudine) in combination with other antiretroviral agents is indicated for:

- the treatment of HIV infection (see DETAILED PHARMACOLOGY: Clinical Trials section).

CONTRAINDICATIONS

- 3TC[®] (lamivudine) 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 3TC[®] and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. However, cases have also been reported in patients with no known risk factors. Treatment with 3TC[®] should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).
- **Post-Treatment Exacerbation of Hepatitis**
It is recommended that all patients with HIV be tested for the presence of chronic hepatitis B virus (HBV) before initiating antiretroviral therapy. 3TC[®] is not indicated for the treatment of chronic HBV infection and the safety and efficacy of 3TC[®] have not been established in patients coinfecting with HBV and HIV. Exacerbations of hepatitis B have been reported in patients after the discontinuation of antiretroviral therapy. Patients coinfecting with HIV and HBV should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment with 3TC[®].
- **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, 3TC[®] should be used with caution. Treatment with 3TC[®] should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur (see ADVERSE REACTIONS section).

General

The safety profile of combination therapy with 3TC[®] (lamivudine) and other antiretroviral agents reflects the individual safety profile of each component. The individual product monographs for each drug in the combination regimen should be consulted before combination therapy is initiated.

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

Trough levels of lamivudine in plasma and of intracellular triphosphate were lower with once-daily dosing than with twice-daily dosing. Furthermore, the C_{max} levels of lamivudine in plasma were higher with once-daily dosing than with twice-daily dosing. (see ACTION AND CLINICAL PHARMACOLOGY section). The clinical significance of these observations is not known.

The clinical status of the patient and the adverse event profile of 3TC[®] should be borne in mind when considering the patient's ability to drive or operate machinery.

Endocrine and Metabolism

Fat Redistribution

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

Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders 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 has been observed in some patients receiving lamivudine. However it is unclear whether this was due to treatment with the medicinal product or to the underlying HIV disease. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of lamivudine until diagnosis of pancreatitis is excluded.

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 3TC[®] should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of 3TC[®] 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 3TC[®] to any patient, and particularly to those with known risk factors for liver disease. Treatment with 3TC[®] should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity (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 3TC[®] have shown that some patients with chronic hepatitis B virus (HBV) disease may experience clinical or laboratory evidence of recurrent hepatitis upon discontinuation of 3TC[®], which may have more severe consequences in patients with decompensated liver disease. If 3TC[®] 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.

Immune

Patients receiving 3TC[®] 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.

Immune Reconstitution

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.

Renal

Patients with Impaired Renal Function

Patients with impaired renal function may be at a greater risk of toxicity from 3TC[®] 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

There are no adequate and well-controlled studies in pregnant women.

Consistent with passive transmission of the drug across the placenta, lamivudine concentrations in infant serum at birth were similar to those in maternal and cord serum. There have been reports of mild, transient elevations in serum lactate levels, which may be due to mitochondrial dysfunction, in neonates and infants exposed *in utero* or peri partum to nucleoside reverse transcriptase inhibitors (NRTIs). The clinical relevance of transient elevations in serum lactate is unknown. There have also been very rare reports of developmental delay, seizures and other neurological disease. However, a causal relationship between these events and NRTI exposure *in utero* or peri partum has not been established. These findings do not affect current recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV. Reproductive studies in animals have not shown evidence of teratogenicity, and have shown no effect on male or female fertility. Lamivudine induced early embryoletality when administered to pregnant rabbits at exposure levels comparable to those achieved in man. Because animal reproductive toxicity studies are not always predictive of the human response, lamivudine should be used during pregnancy only if the potential benefits outweigh the potential risks.

Antiretroviral Pregnancy Registry

To monitor maternal-fetal outcomes of pregnant women exposed to 3TC[®], an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling ViiV Healthcare Shire Canada's Drug Safety Department (1-877-393-8448).

Nursing Women

Following oral administration lamivudine was excreted in breast milk at similar concentrations to those found in serum (1 to 8 µg/mL). It is recommended that mothers taking lamivudine do not breastfeed to avoid risking postnatal transmission of HIV infection and potential adverse effects from lamivudine in nursing infants.

Pediatrics

The safety and pharmacokinetic properties of 3TC[®] in combination with other antiretroviral agents have not been established in pediatric patients who are less than 3 months of age.

ADVERSE REACTIONS

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 3TC[®] (lamivudine) 300 mg once daily or 3TC[®] 150 mg twice daily in combination with RETROVIR[®] 300 mg twice daily and efavirenz 600 mg once daily are listed in Table 1 and Table 2. The most frequent clinical adverse events ($\geq 5\%$ frequency) reported during therapy with 3TC[®] 150 mg b.i.d. plus RETROVIR[®] (AZT[™]) 600 mg per day compared with RETROVIR[®] (AZT[™]) 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	3TC[®] 300 mg q.d. plus RETROVIR[®] plus Efavirenz (n = 272)	3TC[®] 150 mg b.i.d. plus RETROVIR[®] 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	3TC[®] 300 mg q.d. plus RETROVIR[®] plus Efavirenz (n = 272)	3TC[®] 150 mg b.i.d. plus RETROVIR[®] 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 ($\geq 5\%$ Frequency) Reported in Four Controlled Clinical Trials (NUCA3001, NUCA3002, NUCB3001 and NUCB3002)

Adverse Event	3TC[®] 150 mg b.i.d. plus RETROVIR[®] (AZT[™]) (n = 251)	RETROVIR[®] (AZT[™]) (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 3TC[®] 150 mg b.i.d. plus RETROVIR[®] (AZT[™]) 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 B3007.

Six percent (6%) of patients treated with 3TC[®] 150 mg b.i.d. plus RETROVIR[®] (AZT[™]) 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 RETROVIR[®] (AZT[™]) and 13% of patients receiving RETROVIR[®] (AZT[™]) plus zalcitabine. The most frequent adverse events necessitating such permanent discontinuation of therapy with 3TC[®] 150 mg b.i.d. plus RETROVIR[®] (AZT[™]) 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 3TC[®] in Adults

Test (Abnormal Level)	24-Week Surrogate Endpoint Studies (NUCA3001, NUCA3002, NUCB3001, NUCB3002)		Clinical Endpoint Study* (B3007)		Study EPV20001*	
	3TC [®] plus RETROVIR [®]	RETROVIR [®]	3TC [®] plus current therapy†	Placebo plus current therapy†	3TC [®] 300 mg q.d.♣	3TC [®] 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%
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 3TC[®] plus RETROVIR[®] 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 $\geq 5\%$ frequency during therapy with 3TC[®] 4 mg/kg twice daily plus RETROVIR[®] (AZT[™]) 160 mg/m² 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	3TC [®] plus RETROVIR [®] (AZT [™]) (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)	3TC [®] plus RETROVIR [®] (AZT [™])	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 3TC[®] 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 3TC[®]. 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 3TC[®] plus RETROVIR[®] (AZT[™]). Pancreatitis was observed in one patient in this study who received open-label 3TC[®] in combination with RETROVIR[®] (AZT[™]) 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.

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, redistribution/accumulation of body fat (see WARNINGS AND PRECAUTIONS: Fat Redistribution section), 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, lymphadenopathy, neutropenia, splenomegaly, thrombocytopenia
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.

Drug-Drug Interactions

Table 7: Established or Potential Drug-Drug Interactions

Proper name	Effect	Clinical comment
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 3TC [®] /RETROVIR [®] (AZT [™]) combination in patients with renal impairment should be carefully assessed. The effect of co-administration of 3TC [®] with higher doses of co-trimoxazole for the treatment of <i>Pneumocystis carinii</i> pneumonia and toxoplasmosis has not been studied.
Zalcitabine	Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicinal products are used concurrently.	3TC [®] is not recommended to be used in combination with zalcitabine.
Zidovudine	Zidovudine has no effect on the pharmacokinetics of lamivudine (see ACTIONS AND CLINICAL PHARMACOLOGY section)	A modest increase in C _{max} (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 3TC [®] .

DOSAGE AND ADMINISTRATION

3TC[®] therapy should be initiated by a physician experienced in the management of HIV infection.

Recommended Dose and Dosage Adjustment

3TC[®] can be taken with or without food.

Adults and Adolescents:

The recommended oral dose of 3TC[®] (lamivudine) for adults and adolescents who are at least 12 years old is 300 mg daily, administered as either 150 mg twice daily or 300 mg once daily, in combination with other antiretroviral agents (see ACTIONS AND CLINICAL PHARMACOLOGY, WARNINGS AND PRECAUTIONS and CLINICAL TRIALS section).

Pediatrics patients aged \geq 3 months to 12 years:

The recommended oral dose of 3TC[®] for pediatric patients is 4 mg/kg twice daily (up to a maximum of 150 mg twice a day), administered in combination with other antiretroviral agents.

Pediatrics 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 3TC[®] 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.

For adults with low body weight (less than 50 kg or 110 lbs), the recommended oral dose of 3TC[®] is 2 mg/kg twice daily administered in combination with other antiretrovirals.

Table 8: Adjustment of Dosage of 3TC[®] in Accordance With Creatinine Clearance in Adults and Adolescents > 12 years of Age

Creatinine clearance (mL/min)	Recommended Dosage of 3TC[®]
≥ 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 3TC[®] in Accordance with Creatinine Clearance in Children aged 3 months to 12 years

Creatinine clearance (mL/min)	Recommended Dosage of 3TC[®]
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

There is no known antidote for 3TC[®] (lamivudine).

If overdosage occurs the patient should be monitored, and standard supportive treatment applied as required. Although no data is available, administration of activated charcoal may be used to aid in the removal of unabsorbed drug. Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event.

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.

One case of acute overdose in an adult ingesting 6 g of 3TC[®] was reported; there were no clinical signs or symptoms noted and hematologic tests remained normal. One other adult patient in error ingested lamivudine 1,200 mg per day plus zidovudine 1,200 mg per day for approximately 2 weeks; he had a Grade 3 decrease in absolute neutrophil count that resolved upon reduction of doses of lamivudine and zidovudine. Two cases of pediatric overdose were reported in ACTG300. One case was a single dose of 7 mg/kg of 3TC[®]; the second case involved the use of 5 mg/kg of 3TC[®] twice daily for 30 days. There were no clinical signs or symptoms noted in either case.

In Phase I studies, lamivudine was administered at doses up to 20 mg/kg per day (i.e., approximately five times the usual recommended dose in adults) without serious consequences.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Lamivudine is a potent, selective inhibitor of HIV-1 and HIV-2 replication *in vitro*. Lamivudine is the (-) 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. 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.

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 $\mu\text{g/mL}$ (mean \pm 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 3TC[®] 300 mg tablet once daily for 7 days compared to the 3TC[®] 150 mg tablet twice daily for 7 days were assessed in a crossover study in 60 healthy volunteers. 3TC[®] 300 mg once daily resulted in lamivudine exposures that were similar to 3TC[®] 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.

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

3TC[®] tablets should be stored between 2° and 30°C.

3TC[®] oral solution should be stored between 2° and 25°C.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

3TC[®] (lamivudine) tablets 150 mg are white, modified diamond-shaped, scored, film-coated tablets containing 150 mg lamivudine and imprinted with "GX CJ7" on both faces. Available in plastic bottles of 60 tablets.

3TC[®] tablets 300 mg are grey, modified diamond-shaped, film-coated tablets containing 300 mg lamivudine and imprinted with "GX EJ7" on one face. Available in plastic bottles of 30 tablets.

3TC[®] oral solution is a colourless to pale yellow, strawberry-banana flavour, clear liquid containing 10 mg of lamivudine in each 1 mL. Available in plastic bottles of 240 mL.

Tablets

Each 3TC[®] 150 mg tablet contains 150 mg of lamivudine and the nonmedicinal ingredients hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate and titanium dioxide.

Each 3TC[®] 300 mg tablet contains 300 mg of lamivudine and the nonmedicinal ingredients black iron oxide, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate and titanium dioxide.

Oral Solution

Each millilitre of 3TC[®] (lamivudine) 10 mg/mL oral solution contains 10 mg of lamivudine and the nonmedicinal ingredients artificial strawberry and banana flavours, citric acid (anhydrous), hydrochloric acid, methylparaben, propylparaben, propylene glycol, sodium citrate (dihydrate), sodium hydroxide, sucrose, and water. Each 150 mg (15 mL) contains 3 g of sucrose.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

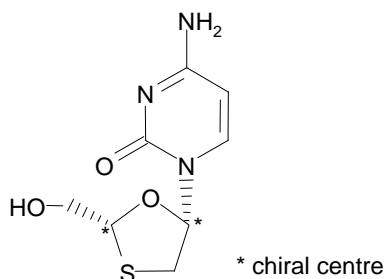
Drug Substance

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: C₈H₁₁N₃O₃S 229.3

Structural formula:



Physicochemical properties:

Description: Lamivudine is a white to off-white crystalline solid with a melting point of 176°C.

Solubility:

Solvent	Temperature (°C)	Solubility (mg/mL)
Water	15	61.3
Water	25	98.1
Methanol	25	33.4
Ethanol	25	11.4
Acetone	25	0.94

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.

Distribution Coefficient: The distribution coefficient between n-octanol and water at pH 7.4 was -0.7 ± 0.2 when measured by HPLC.

CLINICAL TRIALS

Clinical Endpoint Study in Adults

B3007 (CAESAR) was a multicentre, double-blind, placebo-controlled study comparing continued current therapy [RETROVIR® (AZT™) alone (62% of patients) or RETROVIR® (AZT™) with didanosine or zalcitabine (38% of patients)] to the addition of 3TC® or 3TC® 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/mm³ (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)	3TC® plus Current Therapy (n = 896)	3TC® 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 3TC® 300 mg once daily or 3TC® 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	3TC [®] 300 mg q.d. plus RETROVIR [®] plus Efavirenz (n = 278)	3TC [®] 150 mg b.i.d. plus RETROVIR [®] 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 3TC[®] 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 3TC[®] 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 3TC[®] 300 mg once daily (61%) and patients receiving 3TC[®] 150 mg twice daily (62%). Similar increases in median CD4+ cell counts were observed at Week 48 in patients receiving 3TC[®] 300 mg once daily (144 cells/mm³) and patients receiving 3TC[®] 150 mg twice daily (146 cells/mm³).

Clinical Endpoint Study in Pediatric Patients

ACTG300 was a multicentre, randomized, double-blind study that provided for comparison of 3TC[®] plus RETROVIR[®] (AZT[™]) 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/mm³ (mean: 1060 cells/mm³ and range: 0 to 4650 cells/mm³ for patients ≤ 5 years of age; mean: 419 cells/mm³ and range: 0 to 1555 cells/mm³ 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 3TC[®] plus RETROVIR[®] (AZT[™]) 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	3TC [®] plus RETROVIR [®] (AZT [™]) (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%)

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.

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 $1.5 \pm 0.5 \mu\text{g/mL}$ (mean \pm 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 $86\% \pm 16\%$ (mean \pm S.D.) for the 150 mg tablet and $87\% \pm 13\%$ for the oral solution.

The steady-state pharmacokinetic properties of the 3TC[®] 300 mg tablet once daily for 7 days compared to the 3TC[®] (lamivudine) 150 mg tablet twice daily for 7 days were assessed in a crossover study in 60 healthy volunteers. 3TC[®] 300 mg once daily was pharmacokinetically equivalent to 3TC[®] 150 mg twice daily with respect to plasma $\text{AUC}_{24,SS}$. Intracellular lamivudine triphosphate concentrations in peripheral blood mononuclear cells were also pharmacokinetically equivalent with respect to $\text{AUC}_{24,SS}$ and $C_{max24,SS}$.

3TC[®] 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 and 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.

The apparent volume of distribution after IV administration of lamivudine was $1.3 \pm 0.4 \text{ L/kg}$, 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 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.

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 ($T_{1/2}$) ranged from 5 to 7 hours. In one study with extended blood sampling, the mean elimination half-life was 11.9 hours.

Special Populations: 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 13.

Table 13: 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

Pharmacokinetic properties of lamivudine have been assessed as part of a study of 102 HIV-infected patients. A subset of 57 of these patients had pharmacokinetic assessments after oral and IV administration of 1, 2, 4, 8, 12 and 20 mg/kg per day. These patients ranged in age from 4.8 months to 16 years and in weight from 5 to 66 kg. In the 9 infants and children receiving 8 mg/kg per day (the usual recommended pediatric dose), absolute bioavailability was $66\% \pm 26\%$ (mean \pm S.D.), which is less than the $86\% \pm 16\%$ (mean \pm S.D.) observed in adolescents and adults. The mechanism for the diminished absolute bioavailability of lamivudine in infants and children is unknown. Systemic clearance in pediatric patients was higher than in adults and decreased with increasing age in pediatric patients.

After oral administration of 8 mg/kg of lamivudine to 12 pediatric patients, C_{\max} was 1.2 ± 0.5 mcg/mL and half-life was 2.1 ± 0.6 hours (in adults with similar blood sampling, the half-life was 3.7 ± 1 hours). There were no significant differences in pharmacokinetic properties in infants compared with children. There were no significant differences in $T_{1/2}$ across the range of doses. AUC and C_{\max} increased in proportion to dose over the range from 1 to 20 mg/kg. Total exposure to lamivudine, as reflected by AUC, was comparable between pediatric patients receiving an 8 mg/kg dose and adults receiving a 4 mg/kg dose.

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 IC₅₀ and IC₉₀ 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 (zidovudine, zalcitabine, and didanosine) using HIV-1-infected MT-4 cells as the test system. The MTT formazan assay demonstrated synergistic antiretroviral activity between lamivudine and zidovudine, additive antiretroviral activity between lamivudine and zalcitabine, and additive antiretroviral activity between lamivudine and didanosine. The combination of lamivudine/zidovudine also showed synergistic activity in a variable-ratio study.

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-naïve 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-naïve 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-naïve 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, 3TC[®] once daily has been shown to be as effective as 3TC[®] twice daily, and the use of 3TC[®] once daily through 48 weeks does not increase the incidence or the time to emergence of resistance to 3TC[®] 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 \geq 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 log₁₀ copies/mL and 4.6 log₁₀ 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 [³H]-thymidine uptake (Td) assays. In the CP assay, lamivudine was the least toxic of the four compounds. [³H]-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 [³H]-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 F₀ and F₁ generation animals, and the development of the F₁ and F₂ 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

**Pr3TC[®]
lamivudine**

This leaflet is part III of a three-part "Product Monograph" published when 3TC[®] was approved for sale in Canada and is designed specifically for Consumers. Please read this leaflet carefully before you start to take your medicine. This leaflet is a summary and will not tell you everything about 3TC[®]. Contact your doctor or pharmacist if you have any questions about the drug.

3TC[®] (lamivudine) is intended for use in combination with other antiretroviral medicines. Please read the information given with these other medicines before you take 3TC[®].

ABOUT THIS MEDICATION

What the medication is used for:

The name of your medicine is 3TC[®]. 3TC[®] can only be obtained with a prescription from your doctor. 3TC[®] is an antiretroviral medication. It is used together with other antiretroviral medicines to delay the progression of HIV infection.

What it does:

The Human Immunodeficiency Virus (HIV) is a retrovirus. Infection with HIV damages the immune system and can lead to Acquired Immune Deficiency Syndrome (AIDS) and other related illnesses.

3TC[®] is an antiretroviral medication. It is used together with other antiretroviral medicines to delay the progression of HIV infection.

3TC[®] does not cure AIDS or kill the HIV virus, but helps to prevent further damage to the immune system by slowing down the production of new viruses.

When it should not be used:

Do not take 3TC[®] if you are allergic to any ingredient in 3TC[®]. (See What the medicinal ingredient is and What the important nonmedicinal ingredients are sections).

What the medicinal ingredient is:

Each 3TC[®] (150 mg) tablet contains 150 mg of lamivudine. Each 3TC[®] (300 mg) tablet contains 300 mg of lamivudine. 3TC[®] oral solution contains 150 mg of lamivudine in each tablespoon (10 mg in each millilitre).

What the important nonmedicinal ingredients are:

Each 150 mg 3TC[®] tablet also contains hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate and titanium dioxide.

Each 300 mg 3TC[®] tablet also contains black iron oxide, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate and titanium dioxide.

3TC[®] oral solution also contains artificial strawberry and banana flavours, citric acid (anhydrous), hydrochloric acid, methylparaben, propylparaben, propylene glycol, sodium citrate (dihydrate), sodium hydroxide, sucrose and water. Each 150 mg (15 mL) contains 3 g of sucrose.

What dosage forms it comes in:

3TC[®] is available in 150 mg and 300 mg tablets and 10 mg/mL oral solution.

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 3TC[®] without instructions from your doctor as your hepatitis may worsen/reoccur. Your doctor will monitor your condition for several months after stopping treatment with 3TC[®].

Before taking 3TC[®], tell your doctor if:

- You ever had to stop taking this or another medication for this illness because you were allergic to them or they caused problems.
- You have or ever had kidney or liver disease including hepatitis B infection.

Remember that treatment with 3TC[®] 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.

While taking 3TC[®] or any other therapy for HIV disease, you may continue to develop other infections and other complications of HIV infection. Therefore, you should keep in regular contact with the doctor who is treating your condition. Because your medicine helps to control your condition but does not cure it, you will need to take it every day. Do not stop taking your medicine without first talking to your doctor.

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 3TC[®] oral solution contains 3 g of sugar.

Due to the sugar content of 3TC[®] oral solution, you should clean your teeth regularly to reduce the risk of tooth decay.

Use Of This Medicine During Pregnancy And Breastfeeding

If you are pregnant, or likely to become pregnant soon, or if you are breastfeeding, please inform your doctor before taking any drugs, including 3TC[®].

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.

There have been very rare reports of disease that affect the nervous system such as delayed development and seizures.

These findings do not affect current recommendations to use antiretroviral therapy in pregnant women to prevent transmission of HIV to their babies.

It is recommended that HIV-infected women do not breastfeed their infants in order to avoid transmission of HIV. The active substance in 3TC[®] is found in human breast milk. Mothers taking 3TC[®] should not breastfeed their infants.

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. 3TC[®] should not be taken with zalcitabine.

PROPER USE OF THIS MEDICATION

Usual dose:

Take your medicine as your doctor has advised you. The label on it will usually tell you the amount to take, and how frequently. If it does not, or you are not sure, ask your doctor or pharmacist.

3TC[®] can be taken with or without food.

Adults and Adolescents (at least 12 years old): as a general guide, for a twice-a-day dosing, swallow one tablet (150 mg) or one tablespoonful (15 mL) of oral solution, two times a day. For once-a-day dosing, swallow one tablet (300 mg) or two tablespoonfuls (30 mL) of oral solution once a day.

Dosing Schedule	Tablets	Solution
Once a day	One 300 mg tablet	Two tablespoons = 30 mL of solution
Twice a day	One 150 mg tablet	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 (at least 3 months of age): if you are giving 3TC[®] to a child, carefully follow the instructions of your doctor.

Overdose:

Accidentally taking too much of your medicine is unlikely to cause any serious problems. However, you should **immediately** contact your doctor, your hospital emergency department or the nearest poison control centre.

Missed Dose:

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

All medicines may cause some undesirable effects.

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.

3TC[®] 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 body fat have been seen in some patients taking antiretroviral therapy. These changes may include increased amount of fat in the upper back and neck (“buffalo hump”), breasts, and around the trunk. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known at this time.

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 or have any symptoms that you do not understand, you should contact your doctor immediately.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Frequency	Side Effect/ Symptom	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		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 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.		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Frequency	Side Effect/ Symptom	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
	Pancreatitis (inflammation of the pancreas) and symptoms such as severe stomach cramps, nausea, vomiting.			✓

This is not a complete list of side effects. For any unexpected effects while taking 3TC[®], contact your doctor or pharmacist.

HOW TO STORE IT

Store 3TC[®] tablets between 2° and 30°C.
Store 3TC[®] oral solution between 2° and 25°C.

As with all medicines, keep 3TC[®] out of reach of children.

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

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701C
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

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

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 3TC®.

This document plus the full product monograph, prepared for health professionals can be found at:
www.viivhealthcare.com
or by contacting the sponsor, ViiV Healthcare Shire Canada at:
7333 Mississauga Road
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