

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use lamivudine safely and effectively. See full prescribing information for lamivudine.

Lamivudine Tablets

Initial U.S. Approval: 1995

Rx Only

WARNING: LACTIC ACIDOSIS, POSTTREATMENT EXACERBATIONS OF HEPATITIS B IN CO-INFECTED PATIENTS, DIFFERENT FORMULATIONS OF LAMIVUDINE

See full prescribing information for complete boxed warning

- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur. (5.1)
- Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.2)
- Patients with HIV-1 infection should receive only dosage forms of lamivudine appropriate for treatment of HIV-1. (5.2)

RECENT MAJOR CHANGES

Warnings and Precautions, Immune Reconstitution Syndrome (5.6) (11/2011)

INDICATIONS AND USAGE

Lamivudine tablet is a nucleoside analogue reverse transcriptase inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. Limitation of Use: The dosage of this product is for HIV-1 and not for HBV. (1)

DOSE AND ADMINISTRATION

- Adults and adolescents >16 years of age: 300 mg daily, administered as either 150 mg twice daily or 300 mg once daily. (2.1)
- Pediatric patients 3 months up to 16 years of age: Dosage should be based on body weight. (2.2)
- Patients With Renal Impairment: Doses of lamivudine must be adjusted in accordance with renal function. (2.3)

DOSE FORMS AND STRENGTHS

- Tablets: 300 mg (3)
- Tablets: Scored 150 mg (3)

CONTRAINDICATIONS

Lamivudine Tablets are contraindicated in patients with previously demonstrated clinically significant hypersensitivity (e.g., anaphylaxis) to any of the components of the products. (4)

WARNINGS AND PRECAUTIONS

- Lactic acidosis and severe hepatomegaly with steatosis: Reported with the use of nucleoside analogues. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur. (5.1)
- Severe acute exacerbations of hepatitis: Reported in patients who are co-infected with hepatitis B virus and HIV-1 and discontinued lamivudine. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.2)
- Patients with HIV-1 infection should receive only dosage forms of lamivudine appropriate for treatment of HIV-1. (5.2)
- Co-infected HIV-1/HBV Patients: Emergence of lamivudine-resistant HBV variants associated with lamivudine-containing antiretroviral regimens has been reported. (5.2)
- Emtricitabine should not be administered concomitantly with lamivudine-containing products. (5.3)
- Hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving interferon and ribavirin-based regimens. Monitor for treatment-associated toxicities. Discontinue lamivudine as medically appropriate and consider dose reduction or discontinuation of interferon alfa, ribavirin, or both. (5.4)
- Pancreatitis: Use with caution in pediatric patients with a history of pancreatitis or other significant risk factors for pancreatitis. Discontinue treatment as clinically appropriate. (5.5)
- Immune reconstitution syndrome (5.6) and redistribution/accumulation of body fat (5.7) have been reported in patients treated with combination antiretroviral therapy.
- ADVERSE REACTIONS
- The most common reported adverse reactions (incidence ≥15%) in adults were headache, nausea, malaise and fatigue, nasal signs and symptoms, diarrhea, and cough. (6.1)
- The most common reported adverse reactions (incidence ≥15%) in pediatric patients were fever and cough. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Hetero Labs Limited at 866-495-1995 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Zalcitabine is not recommended for use in combination with lamivudine. (7.2)

USE IN SPECIFIC POPULATIONS

Pregnancy: Physicians are encouraged to register patients in the Antiretroviral Pregnancy Registry by calling 1-800-258-4263. (8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: December 2011

FULL PRESCRIBING INFORMATION: CONTENTS*

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

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- Adults and Adolescents >16 years of age
- Pediatric Patients
- Patients With Renal Impairment

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- Lactic Acidosis/Severe Hepatomegaly With Steatosis
- Patients With HIV-1 and Hepatitis B Virus Co-infection
- Use With Other Lamivudine- and Emtricitabine-Containing Products
- Use With Interferon- and Ribavirin-Based Regimens
- Pancreatitis
- Immune Reconstitution Syndrome
- Fat Redistribution

6 ADVERSE REACTIONS

- Clinical Trials Experience
- Postmarketing Experience

7 DRUG INTERACTIONS

- Interferon- and Ribavirin-Based Regimens
- Zalcitabine
- Trimehoprim/Sulfamethoxazole (TMP/SMX)
- Drugs with No Observed Interactions With lamivudine

8 USE IN SPECIFIC POPULATIONS

- Pregnancy
- Nursing Mothers
- Pediatric Use
- Geriatric Use
- Patients With Impaired Renal Function

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- Mechanism of Action
- Pharmacokinetics
- Microbiology

13 NONCLINICAL TOXICOLOGY

- Carcinogenesis, Mutagenesis, Impairment of Fertility
- Reproductive Toxicology Studies

14 CLINICAL STUDIES

- Adults
- Pediatric Patients

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

- Advice for the Patient

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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

Lactic Acidosis and Severe Hepatomegaly: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including lamivudine and other antiretrovirals. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur. See Warnings and Precautions (5.1).

Exacerbations of Hepatitis B: Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue lamivudine and are co-infected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted. See Warnings and Precautions (5.2).

Important Differences Among Lamivudine-Containing Products: Lamivudine Tablets (used to treat HIV-1 infection) contain a higher dose of the active ingredient (lamivudine) than EPVIR-HBV Tablets (used to treat chronic HBV infection). Patients with HIV-1 infection should receive only dosage forms appropriate for treatment of HIV-1. See Warnings and Precautions (5.2).

1 INDICATIONS AND USAGE

Lamivudine Tablet is a nucleoside analogue indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection. Limitation of use: The dosage of this product is for HIV-1 and not for HBV.

2 DOSAGE AND ADMINISTRATION

2.1 Adults and Adolescents >16 years of age

The recommended oral dose of lamivudine in HIV-1-infected adults and adolescents >16 years of age is 300 mg daily, administered as either 150 mg twice daily or 300 mg once daily, in combination with other antiretroviral agents. If lamivudine is administered to a patient infected with HIV-1 and HBV, the dosage indicated for HIV-1 therapy should be used as part of an appropriate combination regimen. See Warnings and Precautions (5.2).

2.2 Pediatric Patients

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

Table 1. Dosing Recommendations for Lamivudine Tablets in Pediatric Patients

Weight (Kg)	Dosage Regimen Using Scored 150 mg Tablet		Total Daily Dose
	AM Dose	PM Dose	
14 to 21	½ tablet (75 mg)	½ tablet (75 mg)	150 mg
>21 to <30	½ tablet (75 mg)	1 tablet (150 mg)	225 mg
>30	1 tablet (150 mg)	1 tablet (150 mg)	300 mg

2.3 Patients With Renal Impairment

Dosing of lamivudine is adjusted in accordance with renal function. Dosage adjustments are listed in Table 2. See Clinical Pharmacology (12.3).

Table 2. Adjustment of Dosage of Lamivudine in Adults and Adolescents (>30 kg) in Accordance With Creatinine Clearance

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

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

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

3 DOSAGE FORMS AND STRENGTHS

• Lamivudine Scored Tablets

150 mg, are white capsule shaped, biconvex, scored film coated tablets debossed with 'J' on one side and '16' on the other side; 1 and 6 separated by a score line.

• Lamivudine Tablets

300 mg, are white capsule shaped, biconvex, film coated tablets debossed with '17' on one side and 'J' on the other side.

4 CONTRAINDICATIONS

Lamivudine tablets are contraindicated in patients with previously demonstrated clinically significant hypersensitivity (e.g., anaphylaxis) to any of the components of the products.

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis/Severe Hepatomegaly With Steatosis

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

5.2 Patients With HIV-1 and Hepatitis B Virus Co-infection

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

Important Differences Among Lamivudine-Containing Products: Lamivudine Tablets contain a higher dose of the same active ingredient (lamivudine) than EPVIR-HBV Tablets. EPVIR-HBV was developed for patients with chronic hepatitis B. The formulation and dosage of lamivudine in EPVIR-HBV are not appropriate for patients co-infected with HIV-1 and HBV. Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients co-infected with HIV-1 and HBV. If treatment with EPVIR-HBV is prescribed for chronic hepatitis B for a patient with unrecognized or untreated HIV-1 infection, rapid emergence of HIV-1 resistance is likely to result because of the subtherapeutic dose and the inappropriateness of monotherapy HIV-1 treatment. If a decision is made to administer lamivudine to patients co-infected with HIV-1 and HBV, lamivudine tablets, COMBIVIR® (lamivudine/zidovudine) Tablets, EPZICOM® (abacavir sulfate and lamivudine) Tablets, or TRIZIVIR® (abacavir sulfate, lamivudine, and zidovudine) Tablets should be used as part of an appropriate combination regimen.

Emergence of Lamivudine-Resistant HBV: In non-HIV-1-infected patients treated with lamivudine for chronic hepatitis B, emergence of lamivudine-resistant HBV has been detected and has been associated with diminished treatment response (see full prescribing information for EPVIR-HBV for additional information).

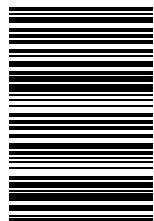
Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been reported in HIV-1-infected patients who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus.

5.3 Use With Other Lamivudine- and Emtricitabine-Containing Products

Lamivudine should not be administered concomitantly with other lamivudine-containing products including EPVIR-HBV Tablets, COMBIVIR (lamivudine/zidovudine) Tablets, EPZICOM (abacavir sulfate and lamivudine) Tablets, or TRIZIVIR (abacavir sulfate, lamivudine, and zidovudine) or emtricitabine-containing products, including ATRILA® (efavirenz, emtricitabine, and tenofovir), EXMTRIVA® (emtricitabine), TRUVADA® (emtricitabine and tenofovir), or COMPLERA™ (rilpivirine/emtricitabine/tenofovir).

5.4 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-1/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV-1/HCV co-infected patients (see Clinical Pharmacology (12.3)), hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin. Patients receiving interferon alfa with or without ribavirin and lamivudine should be closely monitored for treatment-associated toxicities, especially hepatic decompensation.



Lamivudine Tablets
Rx only
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Discontinuation of lamivudine should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Childs-Pugh >6). See the complete prescribing information for interferon alfa and ribavirin.

5.5 Pancreatitis

In pediatric patients with a history of prior antiretroviral nucleoside exposure, a history of pancreatitis, or other significant risk factors for the development of pancreatitis, lamivudine should be used with caution. Treatment with lamivudine should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur (see Adverse Reactions (6.1)).

5.6 Immune Reconstitution Syndrome

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

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré 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.

5.7 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.

6 ADVERSE REACTIONS

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

- Lactic acidosis and severe hepatomegaly with steatosis (see Boxed Warning, Warnings and Precautions (5.1)).
- Severe acute exacerbations of hepatitis B (see Boxed Warning, Warnings and Precautions (5.2)).
- Hepatic decompensation in patients co-infected with HIV-1 and Hepatitis C (see Warnings and Precautions (5.4)).
- Pancreatitis (see Warnings and Precautions (5.5)).

6.1 Clinical Trials Experience

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

Adults - Clinical Trials in HIV-1: The safety profile of lamivudine in adults is primarily based on 3,568 HIV-1-infected patients in 7 clinical trials.

The most common adverse reactions are headache, nausea, malaise, fatigue, nasal signs and symptoms, diarrhea and cough.

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

Table 3. Selected Clinical Adverse Reactions (≥5% Frequency) in Four Controlled Clinical Trials (NUCA3001, NUCA3002, NUCB3001, NUCB3002)

Adverse Reaction	Lamivudine 150 mg Twice Daily plus Zidovudine (n = 251)	Zidovudine ^a (n = 230)
	Body as a Whole	
Headache	35%	27%
Malaise & fatigue	27%	23%
Fever or chills	10%	12%
Digestive		
Nausea	33%	29%
Diarrhea	18%	22%
Nausea & vomiting	13%	12%
Anorexia and/or decreased appetite	10%	7%
Abdominal pain	9%	11%
Abdominal cramps	6%	3%
Dyspepsia	5%	5%
Nervous System		
Neuropathy	12%	10%
Insomnia & other sleep disorders	11%	7%
Dizziness	10%	4%
Depressive disorders	9%	4%
Respiratory		
Nasal signs & symptoms	20%	11%
Cough	18%	13%
Skin		
Skin rashes	9%	6%
Musculoskeletal		
Musculoskeletal pain	12%	10%
Myalgia	8%	6%
Arthralgia	5%	5%

^aEither zidovudine monotherapy or zidovudine in combination with zalcitabine.

Pancreatitis: Pancreatitis was observed in 9 out of 2,613 adult patients (0.3%) who received lamivudine in the controlled clinical trials EPV2001, NUCA3001, NUCB3001, NUCA3002, NUCB3002, and NUCB3007 (see Warnings and Precautions (5.5)).

Lamivudine 300 mg Once Daily: The types and frequencies of clinical adverse reactions reported in patients receiving lamivudine 300 mg once daily or lamivudine 150 mg twice daily (in 3-drug combination regimens in EPV2001 and EPV4001) for 48 weeks were similar.

Selected laboratory abnormalities observed during therapy are summarized in Table 4.

Table 4. Frequencies of Selected Grade 3 to 4 Laboratory Abnormalities in Adults in Four 24-Week Surrogate Endpoint Studies (NUCA3001, NUCA3002, NUCB3001, NUCB3002) and a Clinical End Point Study (NUCB3007)

Test (Threshold Level)	24-Week Surrogate Endpoint Studies ^a	Clinical Endpoint Study ^b		
	Lamivudine plus Zidovudine	Lamivudine plus Current Therapy	Placebo plus Current Therapy ^c	
Absolute neutrophil count (<750/mm ³)	7.2%	5.4%	15%	13%
Hemoglobin (<8.0 g/dL)	2.9%	1.4%	2.2%	3.4%
Platelets (<50,000/mm ³)	0.4%	1.3%	2.8%	1.9%
ALT (>5.0 x ULN)	3.7%	3.6%	3.8%	1.9%
AST (>5.0 x ULN)	1.7%	1.8%	4.0%	2.1%
Bilirubin (>2.5 x ULN)	0.8%	0.4%	ND	ND
Amylase (>2.0 x ULN)	4.2%	1.5%	2.2%	1.1%

^aThe median duration on study was 12 months.

^bEither zidovudine monotherapy or zidovudine in combination with zalcitabine.

^cCurrent therapy was either zidovudine, zidovudine plus didanosine, or zidovudine plus zalcitabine. ULN = Upper limit of normal.

ND = Not done.

The frequencies of selected laboratory abnormalities reported in patients receiving lamivudine 300 mg once daily or lamivudine 150 mg twice daily (in 3-drug combination regimens in EPV2001 and EPV4001) were similar.

Pediatric Patients - Clinical Trials in HIV-1: Selected clinical adverse reactions and physical findings with a ≥5% frequency during therapy with lamivudine 4 mg/kg twice daily plus zidovudine 160 mg/m² 3 times daily in therapy-naïve (536 days of antiretroviral therapy) pediatric patients are listed in Table 5.

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

Adverse Reaction	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%

Adverse Reaction	Lamivudine plus Zidovudine (n = 236)	Didanosine (n = 235)
	Ear, Nose, and Throat	
Signs or symptoms of ears ^a	7%	6%
Nasal discharge or congestion	8%	11%
Other		
Skin rashes	12%	14%
Lymphadenopathy	9%	11%

^aIncludes pain, discharge, erythema, or swelling of an ear.

Pancreatitis: Pancreatitis, which has been fatal in some cases, has been observed in antiretroviral nucleoside-experienced pediatric patients receiving lamivudine alone or in combination with other antiretroviral agents. In an open-label dose-escalation study (NUCA2002), 14 patients (14%) developed pancreatitis while receiving monotherapy with lamivudine. Three of these patients died of complications of pancreatitis. In a second open-label study (NUCA2005), 12 patients (18%) developed pancreatitis. In Study ACTG300, pancreatitis was not observed in 236 patients randomized to lamivudine plus zidovudine. Pancreatitis was observed in 1 patient in this study who received open-label lamivudine in combination with zidovudine and ritonavir following discontinuation of didanosine monotherapy (see Warnings and Precautions (5.5)).

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

elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. In particular, because lamivudine is substantially excreted by the kidney and elderly patients are more likely to have decreased renal function, renal function should be monitored and dosage adjustments should be made accordingly [see Dosage and Administration (2.3), Clinical Pharmacology (12.3)].

8.6 Patients With Impaired Renal Function

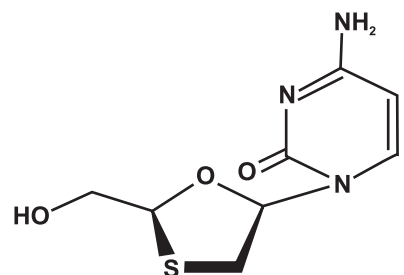
Reduction of the dosage of lamivudine is recommended for patients with impaired renal function [see Dosage and Administration (2.3), Clinical Pharmacology (12.3)].

10 OVERDOSAGE

There is no known antidote for lamivudine. One case of an adult ingesting 6 g of lamivudine was reported; there were no clinical signs or symptoms noted and hematologic tests remained normal. Two cases of pediatric overdose were reported in Study ACTG300. One case involved a single dose of 7 mg/kg of lamivudine; the second case involved use of 5 mg/kg of lamivudine twice daily for 30 days. There were no clinical signs or symptoms noted in either case. Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event. If overdose occurs, the patient should be monitored, and standard supportive treatment applied as required.

11 DESCRIPTION

Lamivudine USP (also known as 3TC), a synthetic nucleoside analogue with activity against HIV-1 and HBV. The chemical name of lamivudine USP is 2(1H)-Pyrimidin-4-amino-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl], (2R-cis)-. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.26. It has the following structural formula:



Lamivudine USP is a white to off white solid and soluble in water. Lamivudine tablets are for oral administration. Each film-coated tablet contains 150 mg or 300 mg of lamivudine USP and the following inactive ingredients: croscopollose, isomalt, isopropyl alcohol, magnesium stearate and methylene chloride. The tablets are coated with opadry white containing hypromellose, polyethylene glycol, polyoxorbate 80 and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lamivudine is an antiviral agent [see Clinical Pharmacology (12.4)].

12.2 Pharmacokinetics

Pharmacokinetics in Adults: The pharmacokinetic properties of lamivudine have been studied in asymptomatic, HIV-1-infected adult patients after administration of single intravenous (IV) doses ranging from 0.25 to 8 mg/kg, as well as single and multiple (twice-daily regimen) oral doses ranging from 0.25 to 10 mg/kg. The pharmacokinetic properties of lamivudine have also been studied as single and multiple oral doses ranging from 5 mg to 600 mg/day administered to HIV-infected patients. The steady-state pharmacokinetics properties of the lamivudine 300-mg tablet once daily for 7 days compared with the lamivudine 150-mg tablet twice daily for 7 days were assessed in a crossover study in 68 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_{0-24} ; however, C_{max} was 66% higher and the trough value was 53% lower compared with the 150-mg twice-daily regimen. Intracellular lamivudine triphosphate exposures in peripheral blood mononuclear cells were also similar with respect to AUC_{0-24} and C_{max} ; however, trough values were lower compared with the 150-mg twice-daily regimen. Inter-subject variability was greater for intracellular lamivudine triphosphate concentrations versus lamivudine plasma trough concentrations. The clinical significance of observed differences for both plasma lamivudine concentrations and intracellular lamivudine triphosphate concentrations is not known.

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

The accumulation ratio of lamivudine in HIV-1-positive asymptomatic adults with normal renal function was 1.50 following 15 days of oral administration of 2 mg/kg twice daily. Effects of Food on Oral Absorption: An investigational 25-mg dosage form of lamivudine was administered orally to 12 asymptomatic, HIV-1-infected patients on 2 occasions, once in the fasted state and once with food (1,099 kcal; 75 grams fat, 34 grams protein, 72 grams carbohydrate). Absorption of lamivudine was slower in the fed state (T_{max} 3.2 ± 1.3 hours) compared with the fasted state (T_{max} 0.9 ± 0.3 hours). C_{max} in the fed state was 49% ± 23% (mean ± SD) lower than in the fasted state. 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.

Distribution: The apparent volume of distribution after IV administration of lamivudine to 20 patients 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 low (<36%). *In vitro* studies showed that over the concentration range of 0.1 to 100 µg/mL, the amount of lamivudine associated with erythrocytes ranged from 53% to 57% and was independent of concentration.

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

Elimination: The majority of lamivudine is eliminated unchanged in urine by active organic cationic secretion. In 9 healthy subjects given a single 300-mg oral dose of lamivudine, renal clearance was 199.7 ± 56.6 mL/min (mean ± SD). In 20 HIV-1-infected patients given a single IV dose, renal clearance was 280.4 ± 75.2 mL/min (mean ± SD), representing 71% ± 16% (mean ± SD) of total clearance of lamivudine. In most single-dose studies in HIV-1-infected patients, HBV-infected patients, or healthy subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life ($t_{1/2}$) ranged from 5 to 7 hours. In HIV-1-infected patients, total clearance was 398.5 ± 69.1 mL/min (mean ± SD). Oral clearance and elimination half-life were independent of dose and body weight over an oral dosing range of 0.25 to 10 mg/kg.

Special Populations: Renal Impairment: The pharmacokinetic properties of lamivudine have been determined in a small group of HIV-1-infected adults with impaired renal function (Table 7).

Table 7. Pharmacokinetic Parameters (Mean ± SD) After a Single 300-mg Oral Dose of Lamivudine in 3 Groups of Adults With Varying in Degrees of Renal Function

Parameter	Creatinine Clearance Criterion (Number of Subjects)		
	>60 mL/min (n = 6)	10-30 mL/min (n = 4)	<10 mL/min (n = 6)
Creatinine clearance (mL/min)	111 ± 14	28 ± 8	6 ± 2
C_{max} (mcg/mL)	2.6 ± 0.5	3.6 ± 0.8	5.8 ± 1.2
AUC ₀₋₂₄ (mcg·hr/mL)	11.0 ± 1.7	48.0 ± 19	157 ± 74
ClV (mL/min)	464 ± 76	114 ± 34	36 ± 11

Exposure (AUC₀₋₂₄), C_{max} , and half-life increased with diminishing renal function (as expressed by creatinine clearance). Apparent total oral clearance (ClV) 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 renal impairment [see Dosage and Administration (2.3)].

Based on a study in otherwise healthy subjects with impaired renal function, hemodialysis increased lamivudine clearance from a mean of 64 to 88 mL/min; however, the length of time of hemodialysis (4 hours) was insufficient to significantly alter mean lamivudine exposure after a single-dose administration. Continuous ambulatory peritoneal dialysis and automated peritoneal dialysis have negligible effects on lamivudine clearance. Therefore, it is recommended, following correction of dose for creatinine clearance, that no additional dose modification be made after routine hemodialysis or peritoneal dialysis.

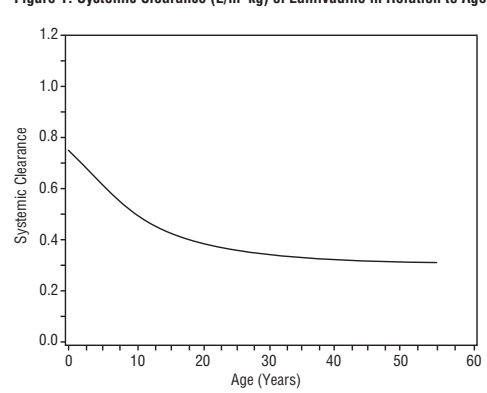
It is not known whether lamivudine can be removed by continuous (24-hour) hemodialysis. The effects of renal impairment on lamivudine pharmacokinetics in pediatric patients are not known.

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

Pediatric Patients: In Study NUCA2002, pharmacokinetic properties of lamivudine were assessed in a subset of 57 HIV-1-infected pediatric patients (age range: 4.8 months to 16 years, weight range: 5 to 66 kg) after oral and IV administration of 1, 2, 4, 8, 12, and 20 mg/kg/day. The mechanism for the diminished absolute bioavailability of lamivudine in infants and children is unknown.

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

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



After oral administration of lamivudine 4 mg/kg twice daily to 11 pediatric patients ranging from 4 months to 14 years of age, C_{max} was 1.1 ± 0.6 mcg/mL and half-life was 2.0 ± 0.6 hours. (In adults with similar blood sampling, the half-life was 3.7 ± 1 hours.) Total exposure to lamivudine, as reflected by mean AUC values, was comparable between pediatric patients receiving an 8-mg/kg/day dose and adults receiving a 4-mg/kg/day dose.

Distribution of lamivudine into cerebrospinal fluid (CSF) was assessed in 38 pediatric patients after multiple oral dosing with lamivudine. CSF samples were collected between 2 and 4 hours postdose. At the dose of 8 mg/kg/day, CSF lamivudine concentrations in 8 patients ranged from 5.6% to 30.9% (mean ± SD of 14.2% ± 9%) of the concentration in a simultaneous serum sample, with CSF lamivudine concentrations ranging from 0.04 to 0.3 mcg/mL.

Limited, uncontrolled pharmacokinetic and safety data are available from administration of lamivudine (and zidovudine) to 36 infants up to 1 week of age in 2 studies in South Africa. In these studies, lamivudine clearance was substantially reduced in 1-week-old neonates relative to pediatric patients (<3 months of age) studied previously. There is insufficient information to establish the time course of changes in clearance between the immediate neonatal period and the age-range >3 months old [see Adverse Reactions (6.1)].

Geriatric Patients: The pharmacokinetics of lamivudine after administration of lamivudine to patients over 65 years of age have not been studied [see Use in Specific Populations (8.5)].

Race: There are no significant gender differences in lamivudine pharmacokinetics.

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

Drug Interactions: Interferon Alfa: There was no significant pharmacokinetic interaction between lamivudine and interferon alfa in a study of 19 healthy male subjects [see Warnings and Precautions (5.4)].

Ribavirin: *In vitro* data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV-1/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n = 18), stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug regimen to HIV-1/HCV co-infected patients [see Warnings and Precautions (6.4)].

Trimethoprim/Sulfamethoxazole: Lamivudine and TMP/SMX were co-administered to 14 HIV-1-positive patients in a single-center, open-label, randomized, crossover study. Each patient received treatment with a single 300-mg dose of lamivudine and TMP 160 mg/SMX 800 mg once a day for 5 days with concomitant administration of lamivudine 300 mg with the fifth dose in a crossover design. Coadministration of TMP/SMX with lamivudine resulted in an increase of 43% ± 23% (mean ± SD) in lamivudine AUC₀₋₂₄, a decrease of 29% ± 13% in lamivudine oral clearance, and a decrease of 30% ± 36% in lamivudine renal clearance. The pharmacokinetic properties of TMP and SMX were not altered by coadministration with lamivudine [see Drug Interactions (7.3)].

Zidovudine: No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-1-infected adult patients given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg q 12 hr) [see Drug Interactions (7.4)].

12.4 Microbiology

Mechanism of Action: Intracellularly, lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is the inhibition of HIV-1 reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue into viral DNA. 3TC-TP is a weak inhibitor of mammalian DNA polymerases α , β , and γ .

Antiviral Activity: The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes) using standard susceptibility assays. EC₅₀ values (50% effective concentrations) were in the range of 0.003 to 154 nM (1 µM = 0.25 mcg/mL). HIV-1 from therapy-naïve subjects with no amino acid substitutions associated with resistance gave median EC₅₀ values of 0.429 µM (range: 0.200 to 2.007 µM) from Virco (n = 92 baseline samples from COLA0263) and 0.25 µM (1.37 to 3.68 µM) from Monogram Biosciences (n = 155 baseline samples from SSS0009). The EC₅₀ values of lamivudine against different HIV-1 clades (A-G) ranged from 0.001 to 0.120 µM, and against HIV-2 isolates from 0.003 to 0.120 µM in peripheral blood mononuclear cells. Ribavirin (50 µM) decreased the anti-HIV-1 activity of lamivudine by 3.5 fold in MT-4 cells. In HIV-1-infected MT-4 cells, lamivudine in combination with zidovudine also exhibited synergistic antiviral activity. Please see the full prescribing information for EPVIR-HBV for information regarding the inhibitory activity of lamivudine against HBV.

Resistance: Lamivudine-resistant variants of HIV-1 have been selected in cell culture. Genotypic analysis showed that the resistance was due to a specific amino acid substitution in the HIV-1 reverse transcriptase at codon 184 changing the methionine to either isoleucine or valine (M184V/I).

HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from patients. Susceptibility of clinical isolates to lamivudine and zidovudine was monitored in controlled clinical trials. In patients receiving lamivudine monotherapy or combination therapy with lamivudine plus zidovudine, HIV-1 isolates from most patients became phenotypically and genotypically resistant to lamivudine within 12 weeks. In some patients harboring zidovudine-resistant virus at baseline, phenotypic sensitivity to zidovudine was restored by 12 weeks of treatment with lamivudine and zidovudine. Combination therapy with lamivudine plus zidovudine delayed the emergence of mutations conferring resistance to zidovudine.

Lamivudine-resistant HBV isolates develop substitutions (rtM204V/I) in the YMDD motif of the catalytic domain of the viral reverse transcriptase. rtM204V/I substitutions are frequently accompanied by other substitutions (rtV173L, rtL180M) which enhance the level of lamivudine resistance or act as compensatory mutations improving replication efficiency. Other substitutions detected in lamivudine-resistant HBV isolates include: rtI80 and rtA181T. Similar HBV mutants have been reported in HIV-1-infected patients who received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus [see Warnings and Precautions (5.2)].

UICSS-Resistance: Lamivudine-resistant HIV-1 mutants were cross-resistant to didanosine (ddI) and zalcitabine (ddC). In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple reverse transcriptase inhibitors, including lamivudine, have emerged.

Genotypic and Phenotypic Analysis of On-Therapy HIV-1 Isolates From Patients With Virologic Failure: Study EPV2007: Fifty-three of 554 (10%) patients enrolled in EPV2007 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 group 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 amino acid substitutions associated with zidovudine resistance (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E), isolates from 10/22 patients contained treatment-emergent amino acid substitutions associated with efavirenz resistance (L100I, K101E, K103N, V108I, or Y181C), and isolates from 8/22 patients contained a treatment-emergent lamivudine resistance-associated substitution (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 substitutions, isolates from 7/22 contained treatment-emergent efavirenz resistance substitutions, and isolates from 5/22 contained treatment-emergent lamivudine resistance substitutions.

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 25- to 295-fold decrease in susceptibility to efavirenz, and isolates from 7/13 patients showed an 85- to 299-fold 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 3/13 patients exhibited a 21- to 342-fold decrease in susceptibility to efavirenz, and isolates from 4/13 patients exhibited a 29- to 199-fold decrease in susceptibility to lamivudine.

Study EPV4001: Fifty patients received zidovudine 300 mg twice daily abacavir 300 mg twice daily plus lamivudine 300 mg once daily and 50 patients received zidovudine 300 mg plus abacavir 300 mg plus lamivudine 150 mg twice daily. The median baseline plasma HIV-1 RNA levels for patients in the 2 groups were 4.79 log₁₀ copies/mL and 4.83 log₁₀ copies/mL, respectively. Fourteen of 50 patients in the lamivudine once-daily treatment group and 9 of 50 patients in the lamivudine twice-daily group were identified as virologic failures.

Genotypic analysis of on-therapy HIV-1 isolates from patients (n = 9) in the lamivudine once-daily treatment group showed that isolates from 6 patients had an abacavir and/or lamivudine resistance-associated substitution M184V alone. On-therapy isolates from patients (n = 6) receiving lamivudine twice daily showed that isolates from 2 patients had M184V alone, and isolates from 2 patients harbored the M184V substitution in combination with zidovudine resistance-associated amino acid substitutions.

Phenotypic analysis of on-therapy isolates from patients (n = 6) receiving lamivudine once daily showed that HIV-1 isolates from 4 patients exhibited a 32- to 53-fold decrease in susceptibility to lamivudine. HIV-1 isolates from these 6 patients were susceptible to zidovudine.

Phenotypic analysis of on-therapy isolates from patients (n = 4) receiving lamivudine twice daily showed that HIV-1 isolates from 1 patient exhibited a 45-fold decrease in susceptibility to lamivudine and a 4.5-fold decrease in susceptibility to zidovudine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) those observed in humans at the recommended therapeutic dose for HIV-1 infection. 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, producing plasma levels of 35 to 45 times those in humans at the recommended dose for HIV-1 infection. In a study of reproductive performance, lamivudine administered to rats at doses up to 4,000 mg/kg/day, producing plasma levels 47 to 70 times those in humans, revealed no evidence of impaired fertility and no effect on the survival, growth, and development to weaning of the offspring.

13.2 Reproductive Toxicology Studies

Reproduction studies have been performed in rats and rabbits at orally administered doses up to 4,000 mg/kg/day and 1,000 mg/kg/day, respectively, producing plasma levels up to approximately 35 times that for the adult HIV dose. No evidence of teratogenicity due to lamivudine was observed. Evidence of early embryolethality was seen in the rabbit at exposure levels similar to those observed in humans, but there was no indication of this effect in the rat at exposure levels up to 35 times those in humans. Studies in pregnant rats and rabbits showed that lamivudine is transferred to the fetus through the placenta.

14 CLINICAL STUDIES

The use of lamivudine is based on the results of clinical studies in HIV-1-infected patients in combination regimens with other antiretroviral agents. Information from trials with clinical endpoints or a combination of CD4+ cell counts and HIV-1 RNA measurements is included below as documentation of the contribution of lamivudine to a combination regimen in controlled trials.

14.1 Adults

Clinical Endpoint Study: NU083007 (CAESAR) was a multi-center, 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 (NNRTI), randomized 1:1:1. A total of 1,816 HIV-1-infected adults with 25 to 520 CD4+ cells/mm³ (median = 172 cells/mm³) at baseline were enrolled; median age was 36 years, 87% were male, 84% were nucleoside-experienced, and 16% were therapy-naïve. The median duration on study was 12 months. Results are summarized in Table 8.

Table 8. Number of Patients (%) With at Least One HIV-1 Disease Progression Event or Death

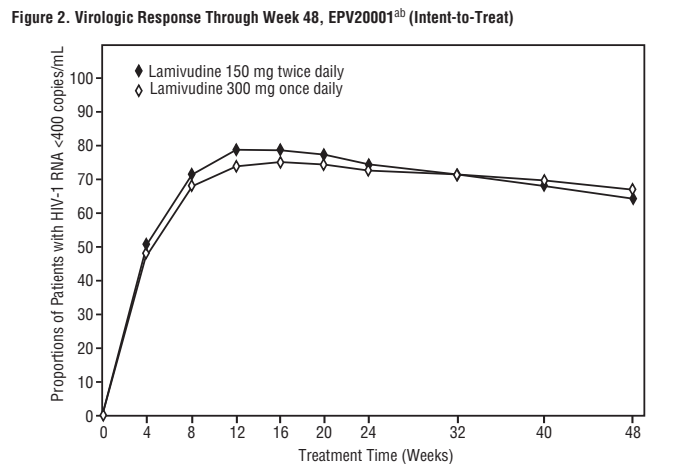
Endpoint	Current Therapy (n = 460)	Lamivudine plus Current Therapy (n = 696)	Lamivudine plus an NNRTI plus Current Therapy (n = 460)
HIV-1 progression or death	90 (19.6%)	86 (9.6%)	41 (8.9%)
Death	27 (5.9%)	23 (2.6%)	14 (3.0%)

^a An investigational non-nucleoside reverse transcriptase inhibitor not approved in the United States.

Surrogate Endpoint Studies: Dual Nucleoside Analogue Studies: Principal clinical trials in the initial development of lamivudine compared lamivudine/zidovudine combinations with zidovudine monotherapy or with zidovudine plus zalcitabine. These studies demonstrated the antiviral effect of lamivudine in a 2-drug combination. More recent uses of lamivudine in treatment of HIV-1 infection incorporate it into multiple-drug regimens containing at least 3 antiretroviral drugs for enhanced viral suppression.

Dose Regimen Comparison Surrogate Endpoint Studies in Therapy-Naïve Adults: EPV2001 was a multi-center, double-blind, controlled study in which patients were randomized 1:1 to receive lamivudine 300 mg once daily plus zidovudine 150 mg twice daily, in combination with zidovudine 300 mg twice daily and efavirenz 600 mg once daily. A total of 554 antiretroviral treatment-naïve HIV-1-infected adults enrolled: male (79%), Caucasian (50%), median age of 35 years, baseline CD4+ cell counts of 69 to 1,089 cells/mm³ (median = 382 cells/mm³), and median plasma HIV-1 RNA of 4.66 log₁₀ copies/mL. Outcomes of treatment through 48 weeks are summarized in Figure 2 and Table 9.

Figure 2. Virologic Response Through Week 48, EPV2001[®] (Intent-to-Treat)



^a Roche AMPLICOR HIV-1 MONITOR.

^b Responders at each visit are patients who had achieved and maintained HIV-1 RNA <400 copies/mL without discontinuation by that visit.

Table 9. Outcomes of Randomized Treatment Through 48 Weeks (Intent-to-Treat)

Outcome	Lamivudine 300 mg Once Daily plus Zidovudine plus Efavirenz (n = 278)	Lamivudine 150 mg Twice Daily plus Zidovudine plus Efavirenz (n = 276)
Responders ^a	67%	65%
Virologic failure ^b	1%	0%
Discontinued due to clinical progression	<1%	8%
Discontinued due to adverse events	6%	12%
Discontinued due to other reasons ^c	18%	14%

^a Achieved confirmed plasma HIV-1 RNA <400 copies/mL and maintained through 48 weeks.

^b Achieved suppression but rebounded by Week 48, discontinued due to virologic failure, insufficient viral response according to the investigator, or never suppressed through week 48.

^c Includes consent withdrawal, lost to follow-up, protocol violation, data outside the study-defined schedule, and randomized but never initiated treatment.

The proportions of patients with HIV-1 RNA <50 copies/mL (via Roche UltraSensitive assay) through Week 48 were 61% for patients receiving lamivudine 300 mg once daily and 63% for patients receiving lamivudine 150 mg twice daily. Median increases in CD4+ cell counts were 144 cells/mm³ at Week 48 in patients receiving lamivudine 300 mg once daily and 146 cells/mm³ for patients receiving lamivudine 150 mg twice daily.

A small, randomized, open-label pilot study, EPV4001, was conducted in Thailand. A total of 159 treatment-naïve adult patients (male 32%, Asian 100%, median age 30 years, baseline mean CD4+ cell count 380 cells/mm³, median plasma HIV-1 RNA 4.8 log₁₀ copies/mL) were enrolled. Two of the treatment arms in this study provided a comparison between lamivudine 300 mg once daily (n = 54) and lamivudine 150 mg twice daily (n = 52), each in combination with zidovudine 300 mg twice daily and abacavir 300 mg twice daily. In intent-to-treat analyses of 48-week data, the proportions of patients with HIV-1 RNA below 400 copies/mL were 61% (33/54) in the group randomized to once-daily lamivudine and 75% (33/52) in the group randomized to receive all 3 drugs twice daily; the proportions with HIV-1 RNA below 50 copies/mL were 54% (29/54) in the once-daily lamivudine group and 67% (35/52) in the all-twice-daily group; and the median increases in CD4+ cell counts were 166 cells/mm³ in the once-daily lamivudine group and 216 cells/mm³ in the all-twice-daily group.

14.2 Pediatric Patients

Clinical Endpoint Study: ACTG300 was a multi-center, randomized, double-blind study that provided for comparison of lamivudine plus RETROVIR (zidovudine) with didanosine monotherapy. A total of 471 symptomatic, HIV-1-infected therapy-naïve (<36 days of antiretroviral therapy) pediatric patients were enrolled in these 2 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: 1,060 cells/mm³ and range: 0 to 4,650 cells/mm³ for patients <5 years of age; mean: 419 cells/mm³ and range: 0 to 1,555 cells/mm³ for patients >5 years of age) and the mean baseline plasma HIV-1 RNA was 5.0 log₁₀ copies/mL. The median duration on study was 10.1 months for the patients receiving lamivudine plus zidovudine and 9.2 months for patients receiving didanosine monotherapy. Results are summarized in Table 10.

Table 10. Number of Patients (%) Reaching a Primary Clinical Endpoint (Disease Progression or Death)

Endpoint	Lamivudine plus Zidovudine (n = 236)	Didanosine (n = 235)
HIV-1 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%)

16 HOW SUPPLIED/STORAGE AND HANDLING

Lamivudine Scored Tablets, 150 mg

White capsule shaped, biconvex, scored film coated tablets debossed with 'J' on one side and '16' on the other side, 1 and 6 separated by a score line.

Bottle of 60 tablets	NDC 31722-753-60
Bottle of 600 tablets	NDC 31722-753-06
Blister Card of 10 Unit-dose tablets	NDC 31722-753-31
Blister pack of 100 (10 x 10) Unit-dose tablets	NDC 31722-753-32