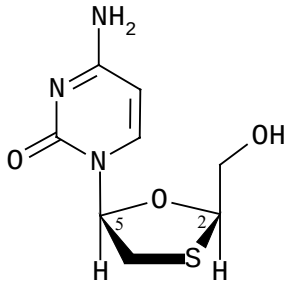
EPIVIR® Tablets
(lamivudine tablets)

EPIVIR® Oral Solution
(lamivudine oral solution)

WARNING: LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING LAMIVUDINE AND OTHER ANTIRETROVIRALS (SEE WARNINGS).

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

DESCRIPTION: EPIVIR (also known as 3TC) is a brand name for lamivudine, a synthetic nucleoside analogue with activity against human immunodeficiency virus-1 (HIV-1) and hepatitis B virus (HBV). The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2′,3′-dideoxy, 3′-thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.3. It has the following structural formula:



Lamivudine is a white to off-white crystalline solid with a solubility of approximately 70 mg/mL in water at 20°C.

EPIVIR Tablets are for oral administration. Each tablet contains 150 mg of lamivudine and the inactive ingredients magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. Opadry YS-1-7706-G White is the coloring agent in the tablet coating.

EPIVIR Oral Solution is for oral administration. One milliliter (1 mL) of EPIVIR Oral Solution contains 10 mg of lamivudine (10 mg/mL) in an aqueous solution and the inactive ingredients artificial strawberry and banana flavors, citric acid (anhydrous), methylparaben, propylene glycol, propylparaben, sodium citrate (dihydrate), and sucrose.

MICROBIOLOGY:

Mechanism of Action: Lamivudine is a synthetic nucleoside analogue. Intracellularly, lamivudine is phosphorylated to its active 5′-triphosphate metabolite, lamivudine triphosphate (L-TP). The principal mode of action of L-TP is inhibition of reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleoside analogue. L-TP is a weak inhibitor of mammalian DNA polymerases α and β, and mitochondrial DNA polymerase.

Antiviral Activity *In Vitro*: The relationship between *in vitro* susceptibility of HIV to lamivudine and the inhibition of HIV replication in humans has not been established. *In vitro* 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. IC_{50} values (50% inhibitory concentrations) were in the range of 2 nM to 15 µM. Lamivudine had anti–HIV-1 activity in all acute virus-cell infections tested. In HIV-1–infected MT-4 cells, lamivudine in combination with zidovudine had synergistic antiretroviral activity. Synergistic activity of lamivudine/zidovudine was also shown in a variable-ratio study. Please see the EPIVIR-HBV package insert for information regarding activity of lamivudine in studies using *in vitro* model systems such as transfected cells for study of HBV replication.

Drug Resistance: Lamivudine-resistant isolates of HIV-1 have been selected *in vitro*. The resistant isolates showed reduced susceptibility to lamivudine and genotypic analysis showed that the resistance was due to specific substitution mutations in the HIV-1 reverse transcriptase at codon 184 from methionine to either isoleucine or valine. HIV-1 strains resistant to both lamivudine and zidovudine have been isolated.

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, phenotypic sensitivity to zidovudine by 12 weeks of treatment was restored. Combination therapy with lamivudine plus zidovudine delayed the emergence of mutations conferring resistance to zidovudine.

Mutations in the HBV polymerase YMDD motif have been associated with reduced susceptibility of HBV to lamivudine *in vitro*. In studies of non-HIV-infected patients with chronic hepatitis B, HBV isolates with YMDD mutations were detected in some patients who received lamivudine daily for 6 months or more, and were associated with evidence of diminished treatment response; similar HBV mutants have been reported in HIV-infected patients who received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus (see PRECAUTIONS).

Cross-Resistance: Cross-resistance among certain reverse transcriptase inhibitors has been observed. Cross-resistance between lamivudine and zidovudine has not been reported. In some patients treated with lamivudine alone or in combination with zidovudine, isolates have emerged with a mutation at codon 184 which confers resistance to lamivudine. In the presence of the 184 mutation, cross-resistance to didanosine and zalcitabine has been seen in some patients; the clinical significance is unknown. In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple reverse transcriptase inhibitors, including lamivudine, have emerged.

CLINICAL PHARMACOLOGY:

Pharmacokinetics in Adults: The pharmacokinetic properties of lamivudine have been studied in asymptomatic, HIV-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 per day administered to HBV-infected patients.

Absorption and Bioavailability: Lamivudine was rapidly absorbed after oral administration in HIV-infected patients. Absolute bioavailability in 12 adult patients was 86% ± 16% (mean ± SD) for the tablet and 87% ± 13% for the oral solution. After oral administration of 2 mg/kg twice a day to 9 adults with HIV, the peak serum lamivudine concentration (C_{max}) was 1.5 ± 0.5 µg/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.

An investigational 25-mg dosage form of lamivudine was administered orally to 12 asymptomatic, HIV-infected patients on 2 occasions, once in the fasted state and once with food (1099 kcal; 75 grams fat, 34 grams protein, 72 grams carbohydrate). Absorption of lamivudine was slower in the fed state (T_{max}: 3.2 ± 1.3 hours) compared with the fasted state (T_{max}: 0.9 ± 0.3 hours); C_{max} in the fed state was 40% ± 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, EPIVIR Tablets and Oral Solution may be administered with or without food.

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

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 6 HIV-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. In 9 healthy subjects given a single 300-mg oral dose of lamivudine, renal clearance was 199.7 ± 56.9 mL/min (mean ± SD). In 20 HIV-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–infected patients, HBV-infected patients, or healthy subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life ($t_{½}$) ranged from 5 to 7 hours. In HIV-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 from 0.25 to 10 mg/kg.

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

Table 1: Pharmacokinetic Parameters (Mean ± SD) After a Single 300-mg Oral Dose of Lamivudine in 3 Groups of Adults With Varying Degrees of Renal Function

Parameter	Creatinine Clearance Criterion (Number of Subjects)		
	>60 mL/min (n = 6)	10-30 mL/min (n = 4)	<10 mL/min (n = 6)
Creatinine clearance (mL/min)	111 ± 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

Exposure (AUC∞), C_{max}, and half-life increased with diminishing renal function (as expressed by creatinine clearance). Apparent total oral clearance (Cl/F) of lamivudine decreased as creatinine clearance decreased. T_{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).

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. Therefore, it is recommended, following correction of dose for creatinine clearance, that no additional dose modification be made after routine hemodialysis.

It is not known whether lamivudine can be removed by peritoneal dialysis or continuous (24-hour) hemodialysis.

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

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

Pediatric Patients: For pharmacokinetic properties of lamivudine in pediatric patients, see PRECAUTIONS: Pediatric Use.

Geriatric Patients: Lamivudine pharmacokinetics have not been specifically studied in patients over 65 years of age.

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

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

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

Lamivudine and trimethoprim/sulfamethoxazole (TMP/SMX) were coadministered to 14 HIV-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 44% ± 23% (mean ± SD) in lamivudine AUC∞, 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.

There was no significant pharmacokinetic interaction between lamivudine and interferon alfa in a study of 19 healthy male subjects.

INDICATIONS AND USAGE: EPIVIR in combination with other antiretroviral agents is indicated for the treatment of HIV infection (see Description of Clinical Studies).

Description of Clinical Studies: ***Clinical Endpoint Study in Adults:*** B3007 (CAESAR) was a multicenter, 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 EPIVIR or EPIVIR plus an investigational non-nucleoside reverse transcriptase inhibitor, randomized 1:2:1. A total of 1816 HIV-infected adults with 25 to 250 CD4 cells/mm^3 (median = 122 cells/mm^3) 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 2.

Table 2: Number of Patients (%) With At Least One HIV Disease Progression Event or Death

Endpoint	Current Therapy (n = 460)	EPIVIR plus Current Therapy (n = 896)	EPIVIR 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 the United States.

Clinical Endpoint Study in Pediatric Patients: ACTG300 was a multicenter, randomized, double-blind study that provided for comparison of EPIVIR plus RETROVIR® (zidovudine) to didanosine monotherapy. A total of 471 symptomatic, HIV-infected therapy-naive (≤56 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/mm^3 (mean: 1060 cells/mm^3 and range: 0 to 4650 cells/mm^3 for patients ≤5 years of age; mean 419 cells/mm^3 and range: 0 to 1555 cells/mm^3 for patients >5 years of age) and the mean baseline plasma HIV RNA was 5.0 $\log_{10}$ copies/mL. The median duration on study was 10.1 months for the patients receiving EPIVIR plus RETROVIR and 9.2 months for patients receiving didanosine monotherapy. Results are summarized in Table 3.

Table 3: Number of Patients (%) Reaching a Primary Clinical Endpoint (Disease Progression or Death)

Endpoint	EPIVIR plus RETROVIR (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%)

Surrogate Endpoint Studies: Therapy-Naive Adults: A3001 was a randomized, double-blind study comparing EPIVIR 150 mg b.i.d. plus RETROVIR 200 mg t.i.d.; EPIVIR 300 mg b.i.d. plus RETROVIR; EPIVIR 300 mg b.i.d.; and RETROVIR. Three hundred sixty-six adults enrolled: male (87%), Caucasian (61%), median age of 34 years, asymptomatic HIV infection (80%), baseline CD4 cell counts of 200 to 500 cells/mm^3 (median = 352 cells/mm^3), and mean baseline plasma HIV RNA of 4.47 (log_{10} copies/mL). B3001 was a randomized, double-blind study comparing EPIVIR 300 mg b.i.d. plus RETROVIR 200 mg t.i.d. versus RETROVIR. One hundred twenty-nine adults enrolled: male (74%), Caucasian (82%), median age of 33 years, asymptomatic HIV infection (64%), and baseline CD4 cell counts of 100 to 400 cells/mm^3 (median = 260 cells/mm^3). Mean changes in CD4 cell count and HIV RNA through 24 weeks of treatment for study A3001 are summarized in Figures 1 and 2, respectively. Mean change in CD4 cell count through 24 weeks of treatment for study B3001 is summarized in Figure 3.

Figure 1: Mean Absolute CD4 Cell Count Change (cells/mm^3) From Baseline in Study A3001

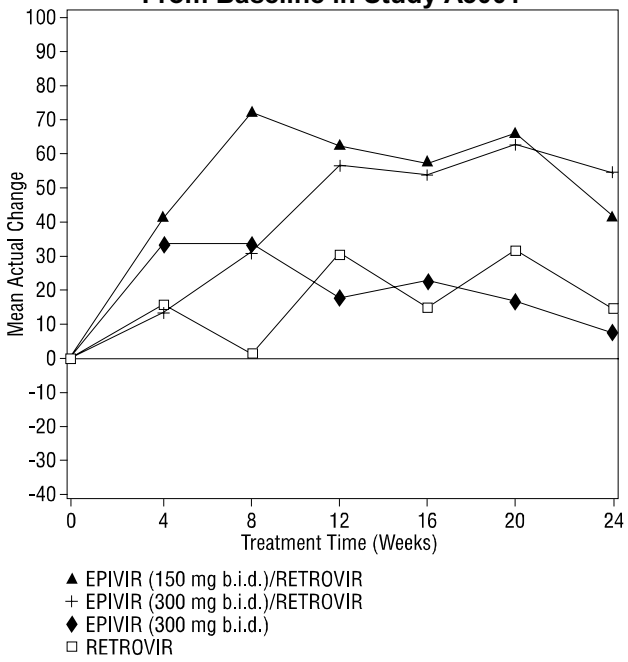


Figure 2: Mean Change From Baseline in Plasma HIV RNA (log_{10} copies/mL) in Study A3001

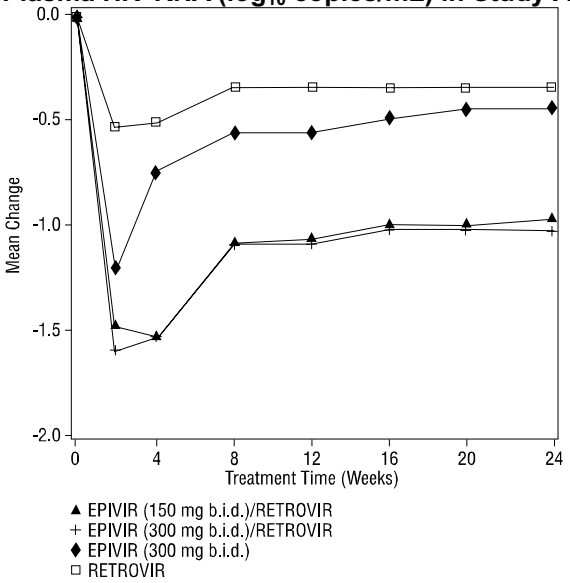
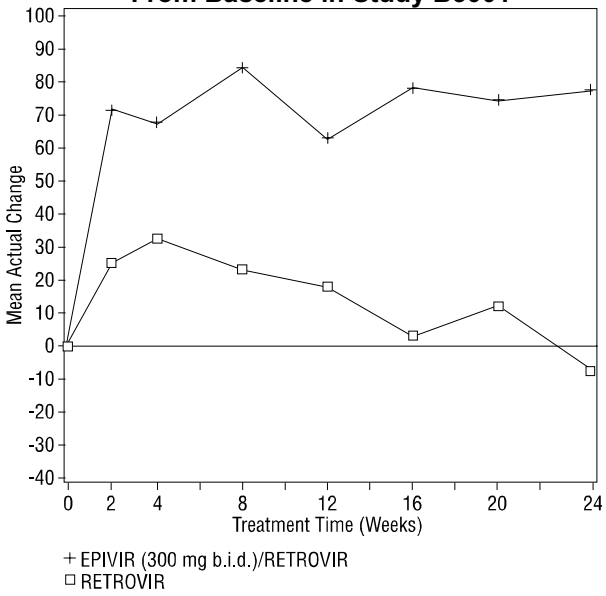


Figure 3: Mean Absolute CD4 Cell Count Change (cells/mm^3) From Baseline in Study B3001



Therapy-Experienced Adults (≥24 Weeks of Prior Zidovudine Therapy): A3002 was a randomized, double-blind study comparing EPIVIR 150 mg b.i.d. plus RETROVIR 200 mg t.i.d.; EPIVIR 300 mg b.i.d. plus RETROVIR; and RETROVIR plus zalcitabine 0.75 mg t.i.d. Two hundred fifty-four adults enrolled: male (83%), Caucasian (63%), median age of 37 years, asymptomatic HIV infection (58%), median duration of prior zidovudine use of 24 months, baseline CD4 cell counts of 100 to 300 cells/mm^3 (median = 211 cells/mm^3), and mean baseline plasma HIV RNA of 4.60 (log_{10} copies/mL). B3002 was a randomized, double-blind study comparing EPIVIR 150 mg b.i.d. plus RETROVIR, EPIVIR 300 mg b.i.d. plus RETROVIR, and RETROVIR. Two hundred twenty-three adults enrolled: male (83%), Caucasian (96%), median age of 36 years, asymptomatic HIV infection (53%), median duration of prior zidovudine

use of 23 months, and baseline CD4 cell counts of 100 to 400 cells/mm^3 (median = 241 cells/mm^3). Mean changes in CD4 cell count and HIV RNA through 24 weeks of treatment in study A3002 are summarized in Figures 4 and 5, respectively. Mean change in CD4 cell count through 24 weeks of treatment for study B3002 is summarized in Figure 6.

Figure 4: Mean Absolute CD4 Cell Count Change (cells/mm^3) From Baseline in Study A3002

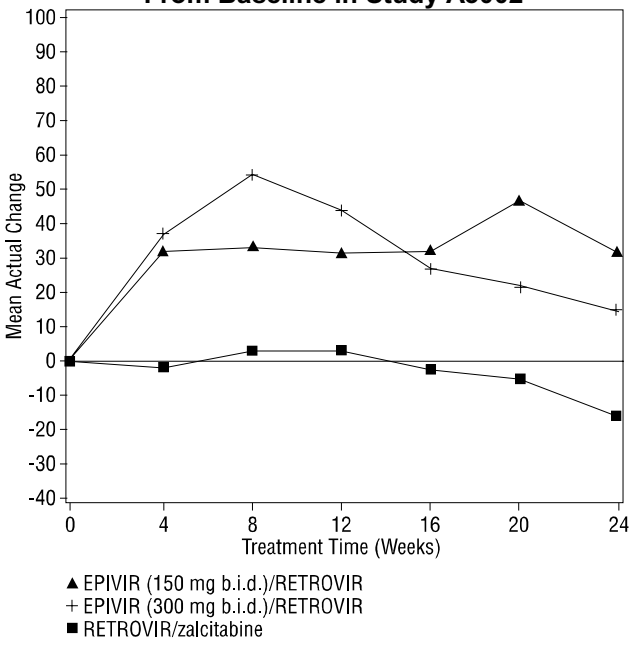


Figure 5: Mean Change From Baseline in Plasma HIV RNA (log_{10} copies/mL) in Study A3002

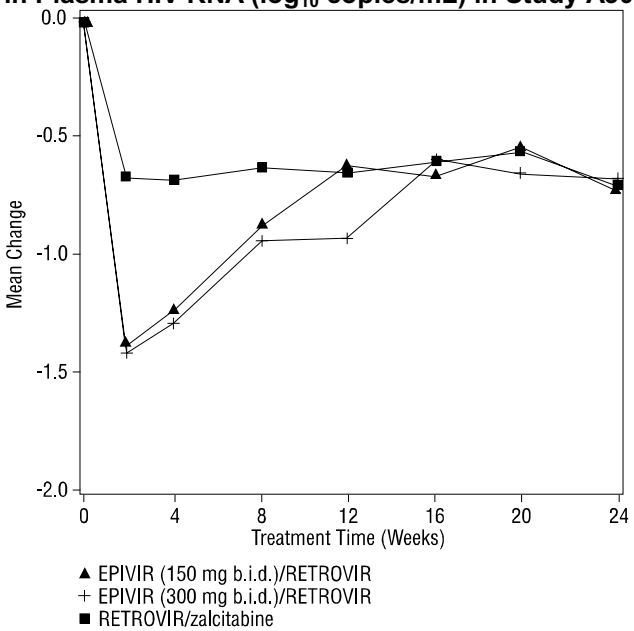
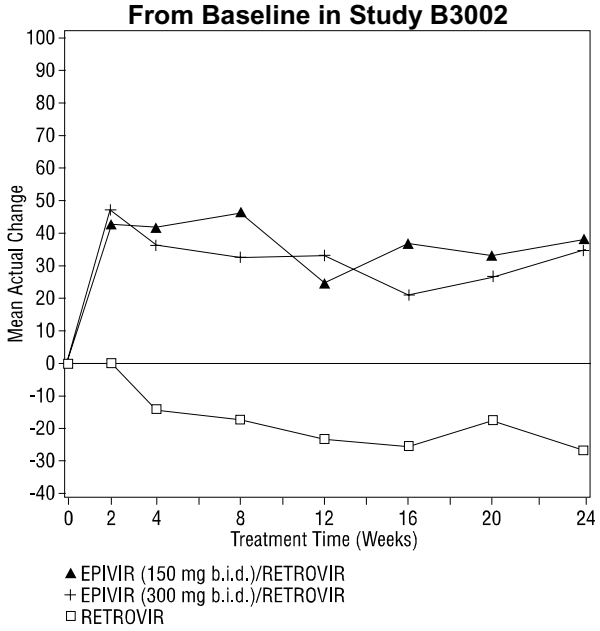


Figure 6: Mean Absolute CD4 Cell Count Change (cells/mm^3) From Baseline in Study B3002



CONTRAINDICATIONS: EPIVIR Tablets and Oral Solution are contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of the products.

WARNINGS: 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, EPIVIR should be used with caution. Treatment with EPIVIR should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur (see ADVERSE REACTIONS).

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 EPIVIR to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with EPIVIR 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).

Important Differences Among Lamivudine-Containing Products: EPIVIR Tablets and Oral Solution contain a higher dose of the same active ingredient (lamivudine) than in EPIVIR-HBV Tablets and Oral Solution. EPIVIR-HBV was developed for patients with chronic hepatitis B. The formulation and dosage of lamivudine in EPIVIR-HBV are not appropriate for patients dually infected with HIV and HBV. Lamivudine has not been adequately studied for treatment of chronic hepatitis B in patients dually infected with HIV and HBV. If treatment with EPIVIR-HBV is prescribed for chronic hepatitis B for a patient with unrecognized or untreated HIV infection, rapid emergence of HIV resistance is likely to result because of the subtherapeutic dose and the inappropriateness of monotherapy HIV treatment. If a decision is made to administer lamivudine to patients dually infected with HIV and HBV, EPIVIR Tablets, EPIVIR Oral Solution, or COMBIVIR® (lamivudine/zidovudine) Tablets should be used as part of an appropriate combination

regimen. COMBIVIR (a fixed-dose combination tablet of lamivudine and zidovudine) should not be administered concomitantly with either EPIVIR, EPIVIR-HBV, or RETROVIR.

Posttreatment Exacerbations of Hepatitis: In clinical trials in non-HIV-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 post-marketing experience after changes from lamivudine-containing HIV treatment regimens to non-lamivudine-containing regimens in patients infected with both HIV and HBV. The causal relationship to discontinuation of lamivudine treatment is unknown. Patients should be closely monitored with both clinical and laboratory followup 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.

PRECAUTIONS:

Patients with Impaired Renal Function: Reduction of the dosage of EPIVIR is recommended for patients with impaired renal function (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Patients with HIV and Hepatitis B Virus Coinfection: Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients dually infected with HIV and HBV. In non-HIV-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 EPIVIR-HBV package insert for additional information). Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been reported in HIV-infected patients who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus.

Information for Patients: EPIVIR is not a cure for HIV infection and patients may continue to experience illnesses associated with HIV infection, including opportunistic infections. Patients should remain under the care of a physician when using EPIVIR. Patients should be advised that the use of EPIVIR has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

Patients should be advised that EPIVIR Tablets and Oral Solution contain a higher dose of the same active ingredient (lamivudine) as EPIVIR-HBV Tablets and Oral Solution. If a decision is made to include lamivudine in the HIV treatment regimen of a patient dually infected with HIV and HBV, the formulation and dosage of lamivudine in EPIVIR (not EPIVIR-HBV) should be used.

Patients should be advised that the long-term effects of EPIVIR are unknown at this time.

EPIVIR Tablets and Oral Solution are for oral ingestion only.

Patients should be advised of the importance of taking EPIVIR exactly as it is prescribed.

Parents or guardians should be advised to monitor pediatric patients for signs and symptoms of pancreatitis.

Drug Interaction: TMP 160 mg/SMX 800 mg once daily has been shown to increase lamivudine exposure (AUC). The effect of higher doses of TMP/SMX on lamivudine pharmacokinetics has not been investigated (see CLINICAL PHARMACOLOGY).

Carcinogenesis, Mutagenesis, and 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

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 2000 mg/kg producing plasma levels of 35 to 45 times those in humans at the recommended dose for HIV infection. In a study of reproductive performance, lamivudine administered to rats at doses up to 4000 mg/kg per 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.

Pregnancy: Pregnancy Category C. Reproduction studies have been performed in rats and rabbits at orally administered doses up to 4000 mg/kg per day and 1000 mg/kg per 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 that in humans. Studies in pregnant rats and rabbits showed that lamivudine is transferred to the fetus through the placenta. There are no adequate and well-controlled studies in pregnant women. Because animal reproductive toxicity studies are not always predictive of human response, lamivudine should be used during pregnancy only if the potential benefits outweigh the risks.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to lamivudine, a Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV infection.

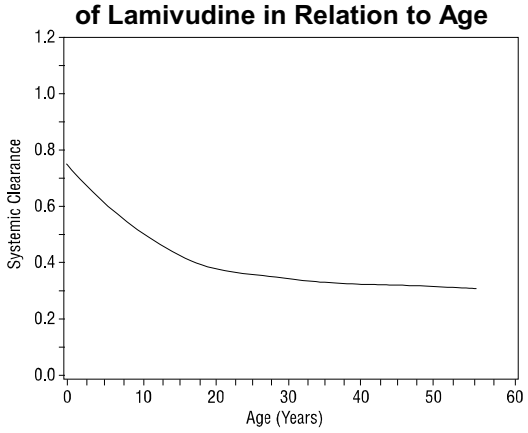
A study in which lactating rats were administered 45 mg/kg of lamivudine showed that lamivudine concentrations in milk were slightly greater than those in plasma. Although it is not known if lamivudine is excreted in human milk, there is the potential for adverse effects from lamivudine in nursing infants. **Mothers should be instructed not to breastfeed if they are receiving lamivudine.**

Pediatric Use: ***HIV:*** The safety and effectiveness of EPIVIR in combination with other antiretroviral agents have been established in pediatric patients 3 months of age and older.

In Study A2002, pharmacokinetic properties of lamivudine were assessed in a subset of 57 HIV-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 per day. In the 9 infants and children (range: 5 months to 12 years of age) receiving oral solution 4 mg/kg twice daily (the usual recommended pediatric dose), absolute bioavailability was 66% ± 26% (mean ± SD), which was less than the 86% ± 16% (mean ± SD) observed in adults. The mechanism for the diminished absolute bioavailability of lamivudine in infants and children is unknown.

Systemic clearance decreased with increasing age in pediatric patients, as shown in Figure 7.

Figure 7: 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 µg/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-per-day dose and adults receiving a 4-mg/kg-per-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 per day, CSF lamivudine concentrations in 8 patients ranged from 5.6% to 30.9% (mean ± SD of 14.2% ± 7.9%) of the concentration in a simultaneous serum sample, with CSF lamivudine concentrations ranging from 0.04 to 0.3 µg/mL.

The effect of renal impairment on lamivudine pharmacokinetics in pediatric patients is not known.

The safety and pharmacokinetic properties of EPIVIR in combination with other antiretroviral agents have not been established in pediatric patients less than 3 months of age.

See INDICATIONS AND USAGE: Description of Clinical Studies, CLINICAL PHARMACOLOGY, WARNINGS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION.

HBV: See the complete prescribing information for EPIVIR-HBV Tablets and Oral Solution for additional information on the pharmacokinetics of lamivudine in HBV-infected children.

ADVERSE REACTIONS:

Clinical Trials in HIV: ***Adults:*** Selected clinical adverse events with a ≥5% frequency during therapy with EPIVIR 150 mg b.i.d. plus RETROVIR 200 mg t.i.d. compared with zidovudine are listed in Table 4.

Table 4: Selected Clinical Adverse Events (≥5% Frequency) in Four Controlled Clinical Trials (A3001, A3002, B3001, B3002)

Adverse Event	EPIVIR 150 mg b.i.d. plus RETROVIR (n = 251)	RETROVIR (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%

Pancreatitis was observed in 3 of the 656 adult patients (<0.5%) who received EPIVIR in controlled clinical trials.

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

Table 5: Frequencies of Selected Laboratory Abnormalities in Adults in Four 24-Week Surrogate Endpoint Studies (A3001, A3002, B3001, B3002) and a Clinical Endpoint Study (B3007)

Test (Abnormal Level)	24-Week Surrogate Endpoint Studies		Clinical Endpoint Study*	
	EPIVIR plus RETROVIR	RETROVIR	EPIVIR plus Current Therapy	Placebo plus Current Therapy†
Neutropenia (ANC<750/mm^3)	7.2%	5.4%	15%	13%
Anemia (Hgb<8.0 g/dL)	2.9%	1.8%	2.2%	3.4%
Thrombocytopenia (platelets<50,000/mm^3)	0.4%	1.3%	2.8%	3.8%
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%

* The median duration on study was 12 months.

† Current therapy was either zidovudine, zidovudine plus didanosine, or zidovudine plus zalcitabine.

ULN = Upper limit of normal.

ANC = Absolute neutrophil count.

ND = Not done.

Pediatric Patients: Selected clinical adverse events and physical findings with a ≥5% frequency during therapy with EPIVIR 4 mg/kg twice daily plus RETROVIR 160 mg/m^2 3 times daily compared with didanosine in therapy-naive (≤56 days of antiretroviral therapy) pediatric patients are listed in Table 6.

Table 6: Selected Clinical Adverse Events and Physical Findings (≥5% Frequency) in Pediatric Patients in Study ACTG300

Adverse Event	EPIVIR plus RETROVIR (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 therapy-naive (≤56 days of antiretroviral therapy) pediatric patients are listed in Table 7.

Table 7: Frequencies of Selected Laboratory Abnormalities in Pediatric Patients in Study ACTG300

Test (Abnormal Level)	EPIVIR plus RETROVIR	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 EPIVIR alone or in combination with other antiretroviral agents. In an open-label dose-escalation study (A2002), 14 patients (14%) developed pancreatitis while receiving monotherapy with EPIVIR. Three of these patients died of complications of pancreatitis. In a second open-label study (A2005), 12 patients (18%) developed pancreatitis. In Study

ACTG300, pancreatitis was not observed in 236 patients randomized to EPIVIR plus RETROVIR. Pancreatitis was observed in 1 patient in this study who received open-label EPIVIR in combination with RETROVIR and ritonavir following discontinuation of didanosine monotherapy.

Paresthesias and peripheral neuropathies were reported in 15 patients (15%) in Study A2002, 6 patients (9%) in Study A2005, and 2 patients (<1%) in Study ACTG300.

Lamivudine in Patients with Chronic Hepatitis B: Clinical trials in chronic hepatitis B used a lower dose of lamivudine (100 mg daily) than the dose used to treat HIV. The most frequent adverse events with lamivudine versus placebo were ear, nose, and throat infections (25% versus 21%); malaise and fatigue (24% versus 28%); and headache (21% versus 21%), respectively. The most frequent laboratory abnormalities reported with lamivudine were elevated ALT, elevated serum lipase, elevated CPK, and posttreatment elevations of liver function tests. Emergence of HBV viral mutants during lamivudine treatment, associated with reduced drug susceptibility and diminished treatment response, was also reported (also see WARNINGS and PRECAUTIONS). Please see the complete prescribing information for EPIVIR-HBV Tablets and Oral Solution for more information.

Observed During Clinical Practice: In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of lamivudine. 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 a combination of their seriousness, frequency of reporting, or potential causal connection to lamivudine.

Digestive: Stomatitis.

Endocrine and Metabolic: Hyperglycemia.

General: Weakness.

Hemic and Lymphatic: Anemia, lymphadenopathy, splenomegaly.

Hepatic and Pancreatic: Lactic acidosis and hepatic steatosis, pancreatitis, posttreatment exacerbation of hepatitis B (see WARNINGS and PRECAUTIONS).

Hypersensitivity: Anaphylaxis, urticaria.

Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.

Nervous: Paresthesia, peripheral neuropathy.

Respiratory: Abnormal breath sounds/wheezing.

Skin: Alopecia, rash, pruritus.

OVERDOSAGE: There is no known antidote for EPIVIR. One case of an adult ingesting 6 g of EPIVIR was reported; there were no clinical signs or symptoms noted and hematologic tests remained normal. Two cases of pediatric overdose were reported in ACTG300. One case was a single dose of 7 mg/kg of EPIVIR; the second case involved use of 5 mg/kg of EPIVIR twice daily for 30 days. There were no clinical signs or symptoms noted in either case. It is not known whether lamivudine can be removed by peritoneal dialysis or hemodialysis.

DOSAGE AND ADMINISTRATION:

Adults: The recommended oral dose of EPIVIR for adults is 150 mg twice daily, administered in combination with other antiretroviral agents. If lamivudine is administered to a patient dually infected with HIV and HBV, the dosage indicated for HIV therapy should be used as part of an appropriate combination regimen (see WARNINGS).

Pediatric Patients: The recommended oral dose of EPIVIR for HIV-infected pediatric patients 3 months up to 16 years of age is 4 mg/kg twice daily (up to a maximum of 150 mg twice a day), administered in combination with other antiretroviral agents.

Dose Adjustment: It is recommended that doses of EPIVIR be adjusted in accordance with renal function (see Table 8). (See CLINICAL PHARMACOLOGY section.)

Table 8: Adjustment of Dosage of EPIVIR in Adults and Adolescents in Accordance With Creatinine Clearance

Creatinine Clearance (mL/min)	Recommended Dosage of EPIVIR
≥50	150 mg twice 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

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

HOW SUPPLIED: EPIVIR Tablets, 150 mg, are white, modified diamond-shaped, film-coated tablets imprinted with “150” on one side and “GX CJ7” on the reverse side. They are available in bottles of 60 tablets (NDC 0173-0470-01) with child-resistant closures.

Store in tightly closed bottles at 25°C (77°F) (see USP Controlled Room Temperature).

EPIVIR Oral Solution, a clear, colorless to pale yellow, strawberry-banana flavored liquid, contains 10 mg of lamivudine in each 1 mL in plastic bottles of 240 mL (NDC 0173-0471-00) with child-resistant closures. This product does not require reconstitution.

Store in tightly closed bottles at 25°C (77°F) (see USP Controlled Room Temperature).

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EPIVIR® Oral Solution Manufactured in England

US Patent No. 5,047,407

January 2001 RL-901