CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-003
21-004

FINAL PRINTED LABELING

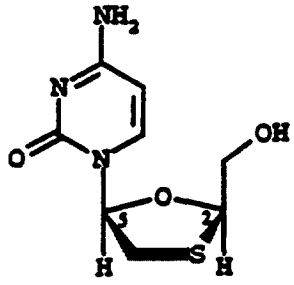
EPIVIR®-HBV™
(lamivudine)
Tablets

EPIVIR®-HBV™
(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).

HUMAN IMMUNODEFICIENCY VIRUS (HIV) COUNSELING AND TESTING SHOULD BE OFFERED TO ALL PATIENTS BEFORE BEGINNING EPIVIR-HBV AND PERIODICALLY DURING TREATMENT (SEE WARNINGS), BECAUSE EPIVIR-HBV TABLETS AND ORAL SOLUTION CONTAIN A LOWER DOSE OF THE SAME ACTIVE INGREDIENT (LAMIVUDINE) AS EPIVIR® TABLETS AND ORAL SOLUTION USED TO TREAT HIV INFECTION. 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 BECAUSE OF SUBTHERAPEUTIC DOSE AND INAPPROPRIATE MONOTHERAPY.

DESCRIPTION: EPIVIR-HBV is a brand name for lamivudine, a synthetic nucleoside analogue with activity against HBV and HIV. Lamivudine was initially developed for the treatment of HIV infection as EPIVIR®. Please see the complete prescribing information for EPIVIR Tablets and Oral Solution for additional information. 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°.

EPIVIR-HBV Tablets are for oral administration. Each tablet contains 100 mg of lamivudine and the inactive ingredients magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. Opadry YS-1-17307-A Butterscotch is the coloring agent in the tablet coating.

EPIVIR-HBV Oral Solution is for oral administration. One milliliter (1 mL) of EPIVIR-HBV Oral Solution contains 5 mg of lamivudine (5 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. Lamivudine is phosphorylated intracellularly to lamivudine triphosphate, L-TP. Incorporation of the monophosphate form into viral DNA by hepatitis B virus (HBV) polymerase results in DNA chain termination. L-TP also inhibits the RNA- and DNA-dependent DNA polymerase activities of HIV-1 reverse transcriptase (RT). L-TP is a weak inhibitor of mammalian alpha-, beta-, and gamma-DNA polymerases.

Antiviral Activity: ***In Vitro:*** *In vitro* activity of lamivudine against HBV was assessed in HBV DNA-transfected 2.2.15 cells, HB611 cells, and infected human primary hepatocytes. IC_{50} values (the concentration of drug needed to reduce the level of extracellular HBV DNA by 50%) varied from 0.01 µM (2.3 ng/mL) to 5.6 µM (1.3 µg/mL) depending upon the duration of exposure of cells to lamivudine, the cell model system, and the protocol used. *In vitro* activity of lamivudine against HIV-1 has been previously demonstrated.

In Vivo: Activity of lamivudine against hepatitis B viruses was evaluated in two animal models. In ducklings chronically infected with duck hepatitis B virus (DHBV), lamivudine administration for 14 days resulted in a decrease of serum DHBV DNA. Increasing levels of serum DHBV DNA were observed within 4 days after cessation of treatment.

In two chimpanzees chronically infected with HBV, lamivudine administration for 28 days resulted in a decrease in serum HBV DNA in one animal and a modest decrease in e antigen (HBeAg) levels in both animals. Treatment of four chimpanzees with escalating doses of lamivudine from 0.1 to 6.0 mg/kg twice daily resulted in a decrease in serum HBV DNA. Within 14 days after cessation of therapy, three chimpanzees tested all showed an increase in HBV DNA serum levels.

Drug Resistance: ***Preclinical Studies: HBV:*** Genotypic analysis of viral isolates obtained from patients who show renewed evidence of replication of HBV while receiving lamivudine suggest that a reduction in sensitivity of HBV to lamivudine is associated with mutations resulting in a methionine to valine or isoleucine substitution in the YMDD motif of the catalytic domain of HBV polymerase (position 552) and a leucine to methionine substitution at position 528. HBV recombinants containing the YMDD mutations are less replication-competent than wild-type HBV *in vitro*. It is not known whether other HBV mutations may be associated with reduced lamivudine susceptibility *in vitro*.

HIV: Lamivudine-resistant isolates of HIV-1 have been selected *in vitro*.

Clinical Studies: HBV: In four controlled clinical trials, YMDD-mutant HBV were detected in 81 of 335 patients receiving lamivudine 100 mg once daily for 52 weeks. The prevalence of YMDD mutations was less than 10% in each of these trials for patients studied at 24 weeks and increased to an average of 24% (range in four studies: 16% to 32%) at 52 weeks. In limited data from a long-term follow-up trial in patients who continued 100 mg/day lamivudine after one of these studies, YMDD mutations further increased from 16% at 1 year to 42% at 2 years. Mutant viruses were associated with evidence of diminished treatment response at 52 weeks relative to lamivudine-treated patients without evidence of YMDD mutations (see PRECAUTIONS). The long-term clinical significance of YMDD-mutant HBV is not known.

HIV: In studies of HIV-1-infected patients who received lamivudine monotherapy or combination therapy with lamivudine plus zidovudine for at least 12 weeks, HIV-1 isolates with reduced *in vitro* susceptibility to lamivudine were detected in most patients (see WARNINGS).

CLINICAL PHARMACOLOGY:

Pharmacokinetics in Adults: The pharmacokinetic properties of lamivudine have been studied as single and multiple oral doses ranging from 5 to 600 mg per day administered to HBV-infected patients.

The pharmacokinetic properties of lamivudine have also 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.

Absorption and Bioavailability: Lamivudine was rapidly absorbed after oral administration in HBV-infected patients and in healthy subjects. Following single oral doses of 100 mg, the peak serum lamivudine concentration (C_{max}) in HBV-infected patients (steady state) and healthy subjects (single dose) was 1.28 ± 0.56 µg/mL and 1.05 ± 0.32 µg/mL (mean ± SD), respectively, which occurred between 0.5 and 2 hours after administration. The area under the plasma concentration versus time curve ($AUC_{[0\text{-}24\ h]}$) following 100 mg lamivudine oral single and repeated daily doses to steady state was 4.3 ± 1.4 (mean ± SD) and 4.7 ± 1.7 µg•h/mL, respectively. The relative bioavailability of the tablet and solution were then demonstrated in healthy subjects. Although the solution demonstrated a slightly higher peak serum concentration (C_{max}), there was no significant difference in systemic exposure (AUC_{∞}) between the solution and the tablet. Therefore, the solution and the tablet may be used interchangeably.

After oral administration of lamivudine once daily to HBV-infected adults, the AUC and peak serum levels (C_{max}) increased in proportion to dose over the range from 5 mg to 600 mg once daily.

The 100-mg tablet was administered orally to 24 healthy subjects on two occasions, once in the fasted state and once with food (standard meal: 967 kcal; 67 grams fat, 33 grams protein, 58 grams carbohydrate). There was no significant difference in systemic exposure (AUC_{∞}) in the fed and fasted states; therefore, EPIVIR-HBV Tablets and Oral Solution may be administered with or without food.

Lamivudine was rapidly absorbed after oral administration in HIV-infected patients. Absolute bioavailability in 12 adult patients was 86% ± 16% (mean ± SD) for the 150-mg tablet and 87% ± 13% for the 10-mg/mL oral solution.

Distribution: The apparent volume of distribution after IV administration of lamivudine to 20 asymptomatic HIV-infected 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%) and independent of dose. *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. In nine healthy subjects receiving 300 mg of lamivudine as single oral doses, a total of 4.2% (range 1.5% to 7.5%) of the dose was excreted as the trans-sulfoxide metabolite in the urine, the majority of which was excreted in the first 12 hours.

Serum concentrations of the trans-sulfoxide metabolite have not been determined.

Elimination: The majority of lamivudine is eliminated unchanged in urine. In nine 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- or 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 healthy subjects and in subjects with impaired renal function, with and without hemodialysis (Table 1):

Table 1: Pharmacokinetic Parameters (Mean ± SD) Dose-Normalized to a Single 100-mg Oral Dose of Lamivudine in Patients With Varying Degrees of Renal Function

Parameter	Creatinine Clearance Criterion (Number of Subjects)		
	≥80 mL/min (n = 9)	20-59 mL/min (n = 8)	<20 mL/min (n = 6)
Creatinine clearance (mL/min)	97 (range 82-117)	39 (range 25-49)	15 (range 13-19)
C_{max} (µg/mL)	1.31 ± 0.35	1.85 ± 0.40	1.55 ± 0.31
AUC_{∞} (µg•h/mL)	5.28 ± 1.01	14.67 ± 3.74	27.33 ± 6.56
Cl/F (mL/min)	326.4 ± 63.8	120.1 ± 29.5	64.5 ± 18.3

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).

Hemodialysis increases 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 is made after routine hemodialysis.

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

The effect of renal impairment on lamivudine pharmacokinetics in pediatric patients with chronic hepatitis B is not known.

Adults With Impaired Hepatic Function: The pharmacokinetic properties of lamivudine have been determined in adults with impaired hepatic function (Table 2). Patients were stratified by severity of hepatic functional impairment.

Table 2: Pharmacokinetic Parameters (Mean ± SD) Dose-Normalized to a Single 100-mg Dose of Lamivudine in Three Groups of Subjects With Normal or Impaired Hepatic Function

Parameter	Normal (n = 8)	Impairment*	
		Moderate (n = 8)	Severe (n = 8)
C_{max} (µg/mL)	0.92 ± 0.31	1.06 ± 0.58	1.08 ± 0.27
AUC_{∞} (µg•h/mL)	3.96 ± 0.58	3.97 ± 1.36	4.30 ± 0.63
T_{max} (h)	1.3 ± 0.8	1.4 ± 0.8	1.4 ± 1.2
Cl/F (mL/min)	424.7 ± 61.9	456.9 ± 129.8	395.2 ± 51.8
Clr (mL/min)	279.2 ± 79.2	323.5 ± 100.9	216.1 ± 58.0

*Hepatic impairment assessed by aminopyrine breath test.

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 EPIVIR-HBV have not been established in the presence of decompensated liver disease (see PRECAUTIONS).

Post-Hepatic Transplant: Fourteen HBV-infected patients received liver transplant following lamivudine therapy and completed pharmacokinetic assessments at enrollment, 2 weeks after 100-mg once-daily dosing (pre-transplant), and 3 months following transplant; there were no significant differences in pharmacokinetic parameters. The overall exposure of lamivudine is primarily affected by renal dysfunction; consequently, transplant patients with reduced renal function had generally higher exposure than patients with normal renal function. Safety and efficacy of EPIVIR-HBV have not been established in this population (see PRECAUTIONS).

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

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

Drug Interactions: Multiple doses of lamivudine and a single dose of interferon were coadministered to 19 healthy male subjects in a pharmacokinetics study. Results indicated a small (10%) reduction in lamivudine AUC, but no change in interferon pharmacokinetic parameters when the two drugs were given in combination. All other pharmacokinetic parameters (C_{max}, T_{max}, and $t_{½}$) were unchanged. There was no significant pharmacokinetic interaction between lamivudine and interferon alfa in this study.

Lamivudine and zidovudine were coadministered to 12 asymptomatic HIV-positive adult patients in a single-center, open-label, randomized, crossover study. No significant differences were observed in AUC_{∞} or total clearance for lamivudine or zidovudine when the two drugs were administered together. Coadministration of lamivudine with zidovudine resulted in an increase of 39% ± 62% (mean ± SD) in C_{max} of zidovudine.

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 (see PRECAUTIONS: Drug Interactions).

INDICATIONS AND USAGE: EPIVIR-HBV is indicated for the treatment of chronic hepatitis B associated with evidence of hepatitis B viral replication and active liver inflammation. This indication is based on 1-year histologic and serologic responses in patients with compensated chronic hepatitis B as described below.

Description of Clinical Studies: The safety and efficacy of EPIVIR-HBV were evaluated in four controlled studies in 967 patients with compensated chronic hepatitis B. All patients were 16 years of age or older and had chronic hepatitis B virus infection (serum HBsAg positive for at least 6 months) accompanied by evidence of HBV replication (serum HBeAg positive and positive for serum HBV DNA, as measured by a research solution-hybridization assay) and persistently elevated ALT levels and/or chronic inflammation on liver biopsy compatible with a diagnosis of chronic viral hepatitis. Three of these studies provided comparisons of EPIVIR-HBV 100 mg once daily versus placebo, and results of these comparisons are summarized below.

- Study 1 was a randomized, double-blind study of EPIVIR-HBV 100 mg once daily versus placebo for 52 weeks, followed by a 16-week no-treatment period, in treatment-naive US patients.
- Study 2 was a randomized, double-blind, three-arm study that compared EPIVIR-HBV 25 mg once daily versus EPIVIR-HBV 100 mg once daily versus placebo for 52 weeks in Asian patients.
- Study 3 was a randomized, partially-blind, three-arm study conducted primarily in North America and Europe in patients who had ongoing evidence of active chronic hepatitis B despite previous treatment with interferon alfa. The study compared EPIVIR-HBV 100 mg once daily for 52 weeks, followed by either EPIVIR-HBV 100 mg or matching placebo once daily for 16 weeks (Arm 1), versus placebo once daily for 68 weeks (Arm 2). (A third arm using a combination of interferon and lamivudine is not presented here because there was not sufficient information to evaluate this regimen.)

Principal endpoint comparisons for the histologic and serologic outcomes in lamivudine (100 mg daily) and placebo recipients in placebo-controlled studies are shown in the following tables.

Table 3: Histologic Response at Week 52 Among Patients Receiving EPIVIR-HBV 100 mg Once Daily or Placebo

	Study 1		Study 2		Study 3	
Assessment	EPIVIR-HBV (n = 62)	Placebo (n = 63)	EPIVIR-HBV (n = 131)	Placebo (n = 68)	EPIVIR-HBV (n = 110)	Placebo (n = 54)
Improvement*	55%	25%	56%	26%	56%	26%
No Improvement	27%	59%	36%	62%	25%	54%
Missing Data	18%	16%	8%	12%	19%	20%

* Improvement was defined as a ≥2-point decrease in the Knodell Histologic Activity Index (HAI)[1] at Week 52 compared with pretreatment HAI. Patients with missing data at baseline were excluded.

Table 4: HBeAg Seroconversion* at Week 52 Among Patients Receiving EPIVIR-HBV 100 mg Once Daily or Placebo

	Study 1		Study 2		Study 3	
Seroconversion	EPIVIR-HBV (n = 63)	Placebo (n = 69)	EPIVIR-HBV (n = 140)	Placebo (n = 70)	EPIVIR-HBV (n = 108)	Placebo (n = 53)
Responder	17%	6%	16%	4%	15%	13%
Nonresponder	67%	78%	80%	91%	69%	68%
Missing Data	16%	16%	4%	4%	17%	19%

* Three-component seroconversion was defined as Week 52 values showing loss of HBeAg, gain of HBeAb, and reduction of HBV DNA to below the solution hybridization assay limit. Subjects with negative baseline HBeAg or HBV DNA assay were excluded from the analysis.

Normalization of serum ALT levels was more frequent with lamivudine treatment compared with placebo in Studies 1-3.

The majority of lamivudine-treated patients showed a decrease of HBV DNA to below the assay limit early in the course of therapy. However, reappearance of assay-detectable HBV DNA during lamivudine treatment was observed in approximately one third of patients after this initial response.

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

WARNINGS:

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. Most of these reports have described patients receiving nucleoside analogues for treatment of HIV infection, but there have been reports of lactic acidosis in patients receiving lamivudine for hepatitis B. Particular caution should be exercised when administering EPIVIR or EPIVIR-HBV 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 or EPIVIR-HBV 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 Between Lamivudine-Containing Products, HIV Testing, and Risk of Emergence of Resistant HIV: EPIVIR-HBV Tablets and Oral Solution contain a lower dose of the same active ingredient (lamivudine) as EPIVIR Tablets and Oral Solution (and COMBIVIR® [lamivudine/zidovudine] Tablets) used to treat HIV infection. The formulation and dosage of lamivudine in EPIVIR-HBV are not appropriate for patients dually infected with HBV and HIV. If a decision is made to administer lamivudine to such patients, the higher dosage indicated for HIV therapy should be used as part of an appropriate combination regimen, and the prescribing information for EPIVIR or COMBIVIR as well as for EPIVIR-HBV should be consulted. HIV counseling and testing should be offered to all patients before beginning EPIVIR-HBV and periodically during treatment because of the risk of rapid emergence of resistant HIV and limitation of treatment options if EPIVIR-HBV is prescribed to treat chronic hepatitis B in a patient who has unrecognized or untreated HIV infection or acquires HIV infection during treatment.

Posttreatment Exacerbations of Hepatitis: Clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of EPIVIR-HBV (these have been primarily detected by serum ALT elevations, in addition to the re-emergence of HBV DNA commonly observed after stopping treatment; see Table 7 for more information regarding frequency of posttreatment ALT elevations). Although most events appear to have been self-limited, fatalities have been reported in some cases. 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 therapy alters the course of posttreatment exacerbations of hepatitis.

Pancreatitis: Pancreatitis has been reported in patients receiving lamivudine, particularly in HIV-infected pediatric patients with prior nucleoside exposure.

PRECAUTIONS:

General: Patients should be assessed before beginning treatment with EPIVIR-HBV by a physician experienced in the management of chronic hepatitis B.

Emergence of Resistance-Associated HBV Mutations: In controlled clinical trials, YMDD-mutant HBV were detected in patients with on-lamivudine re-appearance of HBV DNA after an initial decline below the solution hybridization assay limit (see MICROBIOLOGY: Drug Resistance). These mutations can be detected by a research assay and have been associated with reduced susceptibility to lamivudine *in vitro*. Lamivudine-treated patients with YMDD-mutant HBV at 52 weeks showed diminished treatment responses in comparison to lamivudine-treated patients without evidence of YMDD mutations, including lower rates of HBeAg seroconversion and HBeAg loss (no greater than placebo recipients), more frequent return of positive HBV DNA by solution hybridization assay, and more frequent ALT elevations. In the controlled trials, when patients developed YMDD-mutant HBV, they had a rise in HBV DNA and ALT from their own previous on-treatment levels. Progression of hepatitis B, including death, has been reported in some patients with YMDD-mutant HBV, including patients from the liver transplant setting and from other clinical trials. The long-term clinical significance of YMDD-mutant HBV is not known. Increased clinical and laboratory monitoring may aid in treatment decisions if emergence of viral mutants is suspected.

Limitations of Populations Studied: Safety and efficacy of EPIVIR-HBV have not been established in patients with decompensated liver disease or organ transplants; pediatric patients; patients dually infected with HBV and HCV, hepatitis delta, or HIV; or other populations not included in the principal phase III controlled studies. There are no studies in pregnant women and no data regarding effect on vertical transmission, and appropriate infant immunizations should be used to prevent neonatal acquisition of HBV.

Assessing Patients During Treatment: Patients should be monitored regularly during treatment by a physician experienced in the management of chronic hepatitis B. The safety and effectiveness of treatment with EPIVIR-HBV beyond 1 year have not been established. During treatment, combinations of such events such as return of persistently elevated ALT, increasing levels of HBV DNA over time after an initial decline below assay limit, progression of clinical signs or symptoms of hepatic disease, and/or worsening of hepatic necroinflammatory findings may be considered as potentially reflecting loss of therapeutic response. Such observations should be taken into consideration when determining the advisability of continuing therapy with EPIVIR-HBV.

The optimal duration of treatment, the durability of HBeAg seroconversions occurring during treatment, and the relationship between treatment response and long-term outcomes such as hepatocellular carcinoma or decompensated cirrhosis are not known.

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

Information for Patients: Patients should remain under the care of a physician while taking EPIVIR-HBV. They should discuss any new symptoms or concurrent medications with their physician.

Patients should be advised that EPIVIR-HBV is not a cure for hepatitis B, that the long-term treatment benefits of EPIVIR-HBV are unknown at this time, and, in particular, that the relationship of initial treatment response to outcomes such as hepatocellular carcinoma and decompensated cirrhosis is unknown. Patients should be informed that deterioration of liver disease has occurred in some cases if treatment was discontinued, and that they should discuss any change in regimen with their physician. Patients should be informed that emergence of resistant hepatitis B virus and worsening of disease can occur during treatment, and they should promptly report any new symptoms to their physician.

Patients should be counseled on the importance of testing for HIV to avoid inappropriate therapy and development of resistant HIV, and HIV counseling and testing should be offered before starting EPIVIR-HBV and periodically during therapy. Patients should be advised that EPIVIR-HBV Tablets and EPIVIR-HBV Oral Solution contain a lower dose of the same active ingredient (lamivudine) as EPIVIR Tablets, EPIVIR Oral Solution, and COMBIVIR Tablets. EPIVIR-HBV should not be taken concurrently with EPIVIR or COMBIVIR (see WARNINGS). Patients infected with both HBV and HIV who are planning to change their HIV treatment regimen to a regimen that does not include EPIVIR or COMBIVIR should discuss continued therapy for hepatitis B with their physician.

Patients should be advised that treatment with EPIVIR-HBV has not been shown to reduce the risk of transmission of HBV to others through sexual contact or blood contamination (see Pregnancy section).

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: Lamivudine long-term carcinogenicity studies in mice and rats showed no evidence of carcinogenic potential at exposures up to 34 times (mice) and 200 times (rats) those observed in humans at the recommended therapeutic dose for chronic hepatitis B. 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 60 to 70 times those in humans at the recommended dose for chronic hepatitis B. In a study of reproductive performance, lamivudine administered to rats at doses up to 4000 mg/kg per day, producing plasma levels 80 to 120 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 60 times that for the adult HBV 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 exposures up to 60 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.

Lamivudine has not been shown to affect the transmission of HBV from mother to infant, and appropriate infant immunizations should be used to prevent neonatal acquisition of HBV.

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: A study in lactating rats showed that lamivudine concentrations in milk were similar to 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: ***HBV:*** Safety and efficacy of lamivudine for treatment of chronic hepatitis B in children have not been established. Lamivudine pharmacokinetics were evaluated in a 28-day dose-ranging study in 53 pediatric patients with chronic hepatitis B. Patients aged 2 to 12 years were randomized to receive lamivudine 0.35 mg/kg twice daily, 3 mg/kg once daily, 1.5 mg/kg twice daily, or 4 mg/kg twice daily. Patients aged 13 to 17 years received lamivudine 100 mg once daily. Lamivudine was rapidly absorbed (T_{max} 0.5 to 1 hour). In general, both C_{max} and exposure (AUC) showed dose proportionality in the dosing range studied. In children, weight-corrected oral clearances were higher, resulting in lower AUCs compared with adults. Age-stratified oral clearance was highest at age 2 and declined from 2 to 12 years, where values were then similar to those seen in adults. A dose of 3 mg/kg given once daily produced a steady-state lamivudine AUC (mean 5953 ng•hr/mL ± 1562 SD) similar to that associated with a dose of 100 mg/day in adults.

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

Geriatric Use: Clinical studies of EPIVIR-HBV did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS: Several serious adverse events reported with lamivudine (lactic acidosis and severe hepatomegaly with steatosis, posttreatment exacerbations of hepatitis B, pancreatitis, and emergence of viral mutants associated with reduced drug susceptibility and diminished treatment response) are also described in WARNINGS and PRECAUTIONS.

Clinical Trials in Chronic Hepatitis B: ***Adults:*** Selected clinical adverse events observed with a ≥5% frequency during therapy with EPIVIR-HBV compared with placebo are listed in Table 5. Frequencies of specified laboratory abnormalities during therapy with EPIVIR-HBV compared with placebo are listed in Table 6.

Table 5: Selected Clinical Adverse Events (≥5% Frequency) in Three Placebo-Controlled Clinical Trials During Treatment* (Studies 1-3)

Adverse Event	EPIVIR-HBV (n = 332)	Placebo (n = 200)
Non-site specific		
Malaise and fatigue	24%	28%
Fever or chills	7%	9%
Ear, nose, and throat		
Ear, nose, and throat infections	25%	21%
Sore throat	13%	8%
Gastrointestinal		
Nausea and vomiting	15%	17%
Abdominal discomfort and pain	16%	17%
Diarrhea	14%	12%
Musculoskeletal		
Myalgia	14%	17%
Arthralgia	7%	5%
Neurological		
Headache	21%	21%
Skin		
Skin rashes	5%	5%

*Includes patients treated for 52 to 68 weeks.

Table 6: Frequencies of Specified Laboratory Abnormalities in Three Placebo-Controlled Trials During Treatment* (Studies 1-3)

Test (Abnormal Level)	Patients with Abnormality/Patients with Observations	
	EPIVIR-HBV	Placebo
ALT >3 x baseline†	37/331 (11%)	26/199 (13%)
Albumin <2.5 g/dL	0/331 (0%)	2/199 (1%)
Amylase >3 x baseline	2/259 (<1%)	4/167 (2%)
Serum Lipase ≥2.5 x ULN‡	19/189 (10%)	9/127 (7%)
CPK ≥7 x baseline	31/329 (9%)	9/198 (5%)
Neutrophils <750/mm^3	0/331 (0%)	1/199 (<1%)
Platelets <50,000/mm^3	10/272 (4%)	5/168 (3%)

*Includes patients treated for 52 to 68 weeks.

†See Table 7 for posttreatment ALT values.

‡ Includes observations during and after treatment in the two placebo-controlled trials that collected this information.

ULN = Upper limit of normal.

In patients followed for up to 16 weeks after discontinuation of treatment, posttreatment ALT elevations were observed more frequently in patients who had received EPIVIR-HBV than in patients who had received placebo. A comparison of ALT elevations between weeks 52 and 68 in patients who discontinued

EPIVIR-HBV at week 52 and patients in the same studies who received placebo throughout the treatment course is shown in Table 7.

Table 7: Posttreatment ALT Elevations in Two Placebo-Controlled Studies With No-Active-Treatment Follow-up (Studies 1 and 3)

Abnormal Value	Patients with ALT Elevation/Patients with Observations*	
	EPIVIR-HBV	Placebo
ALT ≥2 x baseline value	37/137 (27%)	22/116 (19%)
ALT ≥3 x baseline value†	29/137 (21%)	9/116 (8%)
ALT ≥2 x baseline value and absolute ALT >500 IU/L	21/137 (15%)	8/116 (7%)
ALT ≥2 x baseline value; and bilirubin >2 x ULN and ≥2 x baseline value	1/137 (0.7%)	1/116 (0.9%)

* Each patient may be represented in one or more category.
† Comparable to a Grade 3 toxicity in accordance with modified WHO criteria.
ULN = Upper limit of normal.

Lamivudine in Patients with HIV: In HIV-infected patients, safety information reflects a higher dose of lamivudine (150 mg b.i.d.) than the dose used to treat chronic hepatitis B in HIV-negative patients. In clinical trials using lamivudine as part of a combination regimen for treatment of HIV infection, several clinical adverse events occurred more often in lamivudine-containing treatment arms than in comparator arms. These included nasal signs and symptoms (20% vs 11%), dizziness (10% vs 4%), and depressive disorders (9% vs 4%). Pancreatitis was observed in three of the 656 adult patients (<0.5%) who received EPIVIR in controlled clinical trials. Laboratory abnormalities reported more often in lamivudine-containing arms included neutropenia and elevations of liver function tests (also more frequent in lamivudine-containing arms for a retrospective analysis of HIV/HBV dually infected patients in one study), and amylase elevations. Please see the complete prescribing information for EPIVIR Tablets and Oral Solution for more information.

Pediatric Patients with Hepatitis B: Limited information on the incidence of adverse events in children (2 to 12 years) and adolescents (13 to 17 years) receiving EPIVIR-HBV Oral Solution or Tablets is available from a 1-month pharmacokinetic study of lamivudine in children and adolescents with chronic hepatitis B. Malaise and fatigue; cough; fever; diarrhea, headache, and viral respiratory infections were the most commonly observed adverse events in lamivudine-treated pediatric patients.

Pediatric Patients with HIV Infection: In early open-label studies of lamivudine in children with HIV, peripheral neuropathy and neutropenia were reported, and pancreatitis was observed in 14% to 15% of patients.

Observed During Clinical Practice: The following events have been identified during post-approval use of lamivudine in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, potential causal connection to lamivudine, or a combination of these factors. Post-marketing experience with lamivudine at this time is largely limited to use in HIV-infected patients.

Digestive: Stomatitis.
Endocrine and Metabolic: Hyperglycemia.
General: Weakness.

Hemic and Lymphatic: Anemia, lymphadenopathy, splenomegaly.

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

Hypersensitivity: Anaphylaxis, urticaria.

Musculoskeletal: Rhabdomyolysis.

Nervous: Paresthesia, peripheral neuropathy.

Respiratory: Abnormal breath sounds/wheezing.

Skin: Alopecia, pruritus, rash.

OVERDOSAGE: There is no known antidote for EPIVIR-HBV. 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. It is not known whether lamivudine can be removed by peritoneal dialysis or hemodialysis.

DOSAGE AND ADMINISTRATION: The recommended oral dose of EPIVIR-HBV for treatment of chronic hepatitis B in adults is 100 mg once daily (see paragraph below and WARNINGS). Safety and effectiveness of treatment beyond 1 year have not been established and the optimum duration of treatment is not known (see PRECAUTIONS).

The formulation and dosage of lamivudine in EPIVIR-HBV are not appropriate for patients dually infected with HBV and HIV. If lamivudine is administered to such patients, the higher dosage indicated for HIV therapy should be used as part of an appropriate combination regimen, and the prescribing information for EPIVIR as well as EPIVIR-HBV should be consulted.

Pediatric Patients: See PRECAUTIONS: Pediatric Use.

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

Table 8: Adjustment of Adult Dosage of EPIVIR-HBV in Accordance With Creatinine Clearance

Creatinine Clearance (mL/min)	Recommended Dosage of EPIVIR-HBV
≥ 50	100 mg once daily
30-49	100 mg first dose, then 50 mg once daily
15-29	100 mg first dose, then 25 mg once daily
5-14	35 mg first dose, then 15 mg once daily
< 5	35 mg first dose, then 10 mg once daily

No additional dosing of EPIVIR-HBV is required after routine (4-hour) hemodialysis. Insufficient data are available to recommend a dosage of EPIVIR-HBV in patients undergoing peritoneal dialysis (see CLINICAL PHARMACOLOGY: Special Populations).

HOW SUPPLIED: EPIVIR-HBV Tablets, 100 mg, are butterscotch-colored, film-coated, biconvex, capsule-shaped tablets imprinted with "GX CG5" on one side.

Bottles of 60 tablets (NDC 0173-0662-00) with child-resistant closures.

Store at controlled room temperature of 20° to 25°C (68° to 77°F) (see USP) in tightly closed bottles.

EPIVIR-HBV Oral Solution, a clear, colorless to pale yellow, strawberry-banana flavored liquid, contains 5 mg of lamivudine in each 1 mL in plastic bottles of 240 mL.

Bottles of 240 mL (NDC 0173-0663-00) with child-resistant closures. This product does not require reconstitution.

Store at controlled room temperature of 20° to 25°C (68° to 77°F) (see USP) in tightly closed bottles.

REFERENCES:

1. Knodell RG, Ishak KG, Black WC, et al. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. *Hepatology*. 1982;1:431-435.

GlaxoWellcome

Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

Manufactured under agreement from
BioChem Pharma Inc.
275 Armand Frappier Blvd.
Laval, Quebec, Canada H7V 4A7

US Patent No. 5,047,407

December 1998 RL-654