PRESCRIBING INFORMATION

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).

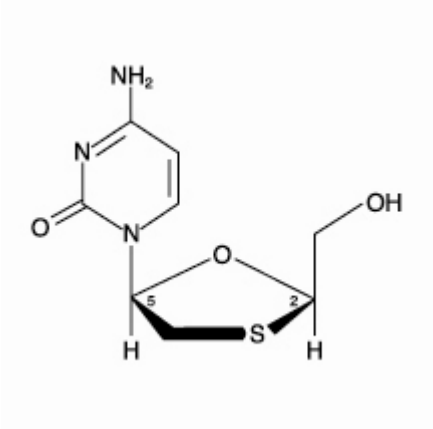
HUMAN IMMUNODEFICIENCY VIRUS (HIV) COUNSELING AND TESTING SHOULD BE OFFERED TO ALL PATIENTS BEFORE BEGINNING EPIVIR-HBV AND PERIODICALLY DURING TREATMENT (SEE WARNINGS), BECAUSE EPIVIR-HBV TABLETS AND ORAL SOLUTION CONTAIN A LOWER DOSE OF THE SAME ACTIVE INGREDIENT (LAMIVUDINE) AS EPIVIR® TABLETS AND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

SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO HAVE DISCONTINUED ANTI-HEPATITIS B THERAPY (INCLUDING EPIVIR-HBV). HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE ANTI-HEPATITIS B THERAPY. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS).

DESCRIPTION

EPIVIR-HBV is a brand name for lamivudine, a synthetic nucleoside analogue with activity against hepatitis B virus (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°C.

EPIVIR-HBV Tablets are for oral administration. Each tablet contains 100 mg of lamivudine and the inactive ingredients hypromellose, macrogol 400, magnesium stearate, microcrystalline cellulose, polysorbate 80, red iron oxide, sodium starch glycolate, titanium dioxide, and yellow iron oxide.

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 (200 mg).

MICROBIOLOGY

Mechanism of Action: Lamivudine is a synthetic nucleoside analogue. Intracellularly, lamivudine is phosphorylated to its active 5′-triphosphate metabolite, lamivudine triphosphate, 3TC-TP. Incorporation of the monophosphate form into viral DNA by HBV reverse transcriptase results in DNA chain termination. 3TC-TP also inhibits the RNA- and DNA-dependent DNA polymerase activities of HIV-1 reverse transcriptase (RT). 3TC-TP is a weak inhibitor of mammalian α, β, and γ-DNA polymerases.

Antiviral Activity: Activity of lamivudine against HBV in cell culture was assessed in HBV DNA-transfected 2.2.15 cells, HB611 cells, and infected human primary hepatocytes. EC_{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 mcg/mL) depending upon the duration of exposure of cells to lamivudine, the cell model system, and the protocol used. See the EPIVIR package insert for information regarding activity of lamivudine against HIV.

Resistance: Lamivudine-resistant isolates were identified in patients with virologic breakthrough, defined when using solution hybridization assay as the detection of HBV DNA in

serum on 2 or more occasions after failing to detect HBV DNA on 2 or more occasions and defined when using PCR assay as a >1 $\log_{10}$ (10-fold) increase in serum HBV DNA from nadir during treatment in a patient who had an initial virologic response.

Lamivudine-resistant HBV isolates develop M204V/I substitutions in the YMDD motif of the catalytic domain of the viral reverse transcriptase. M204V/I substitutions are frequently accompanied by other substitutions (V173L, L180M) which enhance the level of lamivudine resistance or act as compensatory mutations improving replication efficiency. Other substitutions detected in lamivudine-resistant HBV isolates include L80I and A181T.

In 4 controlled clinical trials in adults with HBeAg-positive chronic hepatitis B virus infection (CHB), YMDD-mutant HBV was detected in 81 of 335 patients receiving lamivudine 100 mg once daily for 52 weeks. The prevalence of YMDD substitutions was less than 10% in each of these trials for patients studied at 24 weeks and increased to an average of 24% (range in 4 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 substitutions further increased from 18% (10 of 57) at 1 year to 41% (20 of 49), 53% (27 of 51), and 69% (31 of 45) after 2, 3, and 4 years of treatment, respectively. Over the 5-year treatment period, the proportion of patients who developed YMDD-mutant HBV at any time was 69% (40 of 58).

In a controlled trial in pediatric patients, YMDD-mutant HBV was detected in 31 of 166 (19%) patients receiving lamivudine for 52 weeks. For a subgroup who remained on lamivudine therapy in a follow-up study, YMDD mutations increased from 24% (29 of 121) at 12 months to 59% (68 of 115) at 24 months and 64% (66 of 103) at 36 months of lamivudine treatment.

In a controlled study, treatment-naive patients with HBeAg-positive CHB were treated with lamivudine or lamivudine plus adefovir dipivoxil combination therapy. Following 104 weeks of therapy, YMDD-mutant HBV was detected in 7 of 40 (18%) patients receiving combination therapy compared with 15 of 35 (43%) patients receiving lamivudine-only therapy. In another controlled study, combination therapy was evaluated in adult patients with HBeAg-positive CHB who had YMDD-mutant HBV and diminished clinical and virologic response to lamivudine. Following 52 weeks of lamivudine plus adefovir dipivoxil combination therapy (n = 46) or lamivudine-only therapy (n = 49), YMDD-mutant HBV was detected less frequently in patients receiving combination therapy, 62% vs 96%.

A published study suggested that the rates of lamivudine resistance in patients treated for HBeAg-negative CHB appear to be more variable (0% to 27% at 1 year and 10% to 56% at 2 years).

Cross-Resistance: ***HBV:*** HBV containing lamivudine resistance-associated substitutions (rtL180M, rtM204I, rtM204V, rtL180M + rtM204V, rtV173L + rtL180M + rtM204V) retain susceptibility to adefovir dipivoxil but have reduced susceptibility to entecavir (30 fold) and telbivudine (>100 fold). The lamivudine resistance-associated substitution rtA181T results in diminished response to adefovir and telbivudine. Similarly, HBV with entecavir resistance-associated substitutions (I169T/M250V and T184G/S202I) have >1,000-fold reductions in susceptibility to lamivudine.

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 susceptibility in cell culture 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 mcg/mL and 1.05 ± 0.32 mcg/mL (mean ± SD), respectively, which occurred between 0.5 and 2 hours after administration. The area under the plasma concentration versus time curve ($AUC_{[0\text{-}24\ hr]}$) 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 mcg•hr/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 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 2 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 mcg/mL, the amount of lamivudine associated with erythrocytes ranged from 53% to 57% and was independent of concentration.

Metabolism: Metabolism of lamivudine is a minor route of elimination. In man, the only known metabolite of lamivudine is the trans-sulfoxide metabolite. In 9 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 by active organic cationic secretion. 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- 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} (mcg/mL)	1.31 ± 0.35	1.85 ± 0.40	1.55 ± 0.31
AUC∞ (mcg•hr/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. 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 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 3 Groups of Subjects With Normal or Impaired Hepatic Function

Parameter	Normal (n = 8)	Impairment[a]	
		Moderate (n = 8)	Severe (n = 8)
C_{max} (mcg/mL)	0.92 ± 0.31	1.06 ± 0.58	1.08 ± 0.27
AUC∞ (mcg•hr/mL)	3.96 ± 0.58	3.97 ± 1.36	4.30 ± 0.63
T_{max} (hr)	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

[a] 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).

Pediatric Patients: 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. Weight-corrected 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 5,953 ng•hr/mL ± 1,562 SD) similar to that associated with a dose of 100 mg/day in adults.

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 2 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 2 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).

Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another. Therefore, use of lamivudine in combination with zalcitabine is not recommended.

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 adult patients with compensated chronic hepatitis B, and

more limited information from a study in pediatric patients ages 2 to 17 years (see Description of Clinical Studies below).

The following point should be considered when initiating therapy with EPIVIR-HBV:

- Due to high rates of resistance development in treated patients, initiation of lamivudine treatment should only be considered when the use of an alternative antiviral agent with a higher genetic barrier to resistance is not available or appropriate.

Description of Clinical Studies: ***Adults:*** The safety and efficacy of EPIVIR-HBV were evaluated in 4 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, 3-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, 3-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 Adult 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[a]	55%	25%	56%	26%	56%	26%
No Improvement	27%	59%	36%	62%	25%	54%

Missing Data	18%	16%	8%	12%	19%	20%

[a] 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[a] at Week 52 Among Adult 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%

[a] 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.

Pediatrics: The safety and efficacy of EPIVIR-HBV were evaluated in a double-blind clinical trial in 286 patients ranging from 2 to 17 years of age, who were randomized (2:1) to receive 52 weeks of lamivudine (3 mg/kg once daily to a maximum of 100 mg once daily) or placebo. All patients had compensated chronic hepatitis B accompanied by evidence of hepatitis B virus replication (positive serum HBeAg and positive for serum HBV DNA by a research branched-chain DNA assay) and persistently elevated serum ALT levels. The combination of loss of HBeAg and reduction of HBV DNA to below the assay limit of the research assay, evaluated at Week 52, was observed in 23% of lamivudine subjects and 13% of placebo subjects. Normalization of serum ALT was achieved and maintained to Week 52 more frequently in patients treated with EPIVIR-HBV compared with placebo (55% versus 13%). As in the adult controlled trials, most lamivudine-treated subjects had decreases in HBV DNA below the assay limit early in treatment, but about one third of subjects with this initial response had reappearance of assay-detectable HBV DNA during treatment. Adolescents (ages 13 to 17 years) showed less evidence of treatment effect than younger children.

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, COMBIVIR® (lamivudine/zidovudine) Tablets, EPZICOM® (abacavir sulfate and lamivudine) Tablets, and TRIZIVIR® (abacavir, lamivudine, and 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, COMBIVIR, EPZICOM, or TRIZIVIR 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 (adult and pediatric) 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 or branched-chain DNA 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. In clinical practice, monitoring of ALT and HBV DNA levels during lamivudine treatment 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 <2 years of age; 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: A Patient Package Insert (PPI) for EPIVIR-HBV is available for patient information.

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 when treatment was discontinued. Patients should be advised to discuss any changes 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, COMBIVIR Tablets, EPZICOM Tablets, and TRIZIVIR Tablets. EPIVIR-HBV should not be taken concurrently with EPIVIR, COMBIVIR, EPZICOM, or TRIZIVIR (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, COMBIVIR, EPZICOM, or TRIZIVIR 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).

Diabetic patients should be advised that each 20-mL dose of EPIVIR-HBV Oral Solution contains 4 grams of sucrose.

Drug Interactions: Lamivudine is predominantly eliminated in the urine by active organic cationic secretion. The possibility of interactions with other drugs administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system (e.g., trimethoprim).

TMP 160 mg/SMX 800 mg once daily has been shown to increase lamivudine exposure (AUC) by 44% (see CLINICAL PHARMACOLOGY). No change in dose of either drug is

recommended. There is no information regarding the effect on lamivudine pharmacokinetics of higher doses of TMP/SMX such as those used to treat *Pneumocystis carinii* pneumonia. No data are available regarding interactions with other drugs that have renal clearance mechanisms similar to that of lamivudine.

Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another. Therefore, use of lamivudine in combination with zalcitabine is not recommended.

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 2,000 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 4,000 mg/kg/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 4,000 mg/kg/day and 1,000 mg/kg/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 administered 45 mg/kg of lamivudine showed that lamivudine concentrations in milk were slightly greater than those in plasma. Lamivudine is also excreted in human milk. Samples of breast milk obtained from 20 mothers receiving lamivudine monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice daily and 300 mg zidovudine twice daily) had measurable concentrations of lamivudine.

Because of the potential for serious adverse reactions 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 been studied in pediatric patients from 2 to 17 years of age in a controlled clinical trial (see CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, and DOSAGE AND ADMINISTRATION).

Safety and efficacy in pediatric patients <2 years of age have not been established.

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. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. 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 PRECAUTIONS: Patients with Impaired Renal Function and 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 3 Placebo-Controlled Clinical Trials in Adults During Treatment[a] (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%

[a] Includes patients treated for 52 to 68 weeks.

Table 6. Frequencies of Specified Laboratory Abnormalities in 3 Placebo-Controlled Trials in Adults During Treatment[a] (Studies 1-3)

Test (Abnormal Level)	Patients With Abnormality/Patients With Observations	
	EPIVIR-HBV	Placebo
ALT >3 x baseline[b]	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[c]	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%)

[a] Includes patients treated for 52 to 68 weeks.

[b] See Table 7 for posttreatment ALT values.

[c] Includes observations during and after treatment in the 2 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 2 Placebo-Controlled Studies in Adults With No-Active-Treatment Follow-up (Studies 1 and 3)

Abnormal Value	Patients With ALT Elevation/ Patients With Observations[a]	
	EPIVIR-HBV	Placebo
ALT ≥2 x baseline value	37/137 (27%)	22/116 (19%)
ALT ≥3 x baseline value[b]	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%)

[a] Each patient may be represented in one or more category.

[b] 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 9 of the 2,613 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: Most commonly observed adverse events in the pediatric trials were similar to those in adult trials; in addition, respiratory symptoms (cough, bronchitis, and viral respiratory infections) were reported in both lamivudine and placebo recipients. Posttreatment transaminase elevations were observed in some patients followed after cessation of lamivudine.

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 (including pure red cell aplasia and severe anemias progressing on therapy), 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. 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.

DOSAGE AND ADMINISTRATION

Adults: 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: The recommended oral dose of EPIVIR-HBV for pediatric patients 2 to 17 years of age with chronic hepatitis B is 3 mg/kg once daily up to a maximum daily dose of 100 mg. Safety and effectiveness of treatment beyond 1 year have not been established and the optimum duration of treatment is not known (see PRECAUTIONS).

EPIVIR-HBV is available in a 5-mg/mL oral solution when a liquid formulation is needed. (Please see information above regarding distinctions between different lamivudine-containing products.)

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 or peritoneal dialysis.

Although there are insufficient data to recommend a specific dose adjustment of EPIVIR-HBV in pediatric patients with renal impairment, a dose reduction should be considered.

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 25°C (77°F), excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

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.

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GlaxoSmithKline
Research Triangle Park, NC 27709

Manufactured under agreement from
Shire Pharmaceuticals Group plc
Basingstoke, UK

Month year EPH:xPI

PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

PATIENT INFORMATION

EPIVIR-HBV® (lamivudine) Tablets
EPIVIR-HBV® (lamivudine) Oral Solution

Please read this information before you start taking EPIVIR-HBV (pronounced EP-i-veer h-b-v). Re-read it each time you get your prescription, in case some information has changed. **This information does not take the place of careful discussions with your doctor when you start this medication and at checkups. Stay under a doctor's care when you take EPIVIR-HBV and do not change or stop treatment without first talking with your doctor.**

What is EPIVIR-HBV?
EPIVIR-HBV is the brand name of a product that contains lamivudine, a drug used to treat chronic hepatitis B in patients with actively growing virus and liver inflammation. Hepatitis B can cause damage to cells in the liver. Eventually, this can scar the liver.

The lamivudine in EPIVIR-HBV can reduce the ability of the hepatitis B virus to multiply and infect new liver cells. It may help to lower the amount of hepatitis B virus in your body.

EPIVIR-HBV contains a lower dose of lamivudine than the dose in EPIVIR®, COMBIVIR®, EPZICOM®, and TRIZIVIR®.

Why should I consider HIV testing before starting treatment with EPIVIR-HBV?

Your doctor or healthcare provider should offer you counseling and testing for HIV infection (sometimes called the AIDS virus) before treatment for hepatitis B is started with EPIVIR-HBV, and periodically during treatment. EPIVIR-HBV Tablets and EPIVIR-HBV Oral Solution contain a lower dose of the medicine than other lamivudine-containing drugs, such as EPIVIR, COMBIVIR, EPZICOM, and TRIZIVIR which are used to treat HIV. Treatment with EPIVIR-HBV in HIV-infected patients may cause the HIV virus to be less treatable with lamivudine and some other drugs.

If I am HIV-positive, can I take EPIVIR-HBV?

People who have both chronic hepatitis B and HIV should not take EPIVIR-HBV. EPIVIR-HBV Tablets and EPIVIR-HBV Oral Solution contain a lower dose of the same drug (lamivudine) as EPIVIR Tablets, EPIVIR Oral Solution, COMBIVIR Tablets, EPZICOM Tablets, and TRIZIVIR Tablets. If you have both hepatitis B and HIV, make sure that your doctor or healthcare provider is aware that you have both infections. If you are prescribed lamivudine as part of your combination treatment for HIV, you should use only the products and doses that are intended for treatment of HIV infection, because the lower dose of lamivudine in EPIVIR-HBV could cause the HIV virus to be less responsive to treatment. If you are planning to change your HIV treatment to a regimen that does not include EPIVIR, COMBIVIR, EPZICOM, or TRIZIVIR, you should first discuss this change with your doctor or healthcare provider.

Does EPIVIR-HBV cure hepatitis B infection?

EPIVIR-HBV is not a cure for hepatitis B. In studies comparing EPIVIR-HBV with placebo (an inactive sugar pill) for 1 year, more people treated with EPIVIR-HBV had reductions in liver inflammation. It is not known whether EPIVIR-HBV will reduce the risk of getting liver cancer or cirrhosis that may be caused by the hepatitis B virus.

In studies, some patients developed hepatitis B viruses that are resistant to EPIVIR-HBV. These patients generally had less benefit from treatment with EPIVIR-HBV. Some patients have had worsening of hepatitis after resistant virus appears. The long-term importance of a resistant virus is not known.

What happens if I stop taking EPIVIR-HBV?

After stopping treatment with EPIVIR-HBV, some patients have had symptoms or blood tests showing that their hepatitis has gotten worse. Therefore, your doctor should check your health, which may include blood tests, for at least several months after stopping treatment with

EPIVIR-HBV. Tell your doctor right away about any new or unusual symptoms that you notice after stopping treatment.

Who should not take EPIVIR-HBV?

You should not take EPIVIR-HBV if you have or may have HIV infection (sometimes called the AIDS virus). EPIVIR-HBV does not contain an appropriate dose of lamivudine for treatment of HIV infection, and using EPIVIR-HBV could cause the HIV virus to become less treatable with lamivudine and some other drugs.

You should not take EPIVIR-HBV if you are also taking EPIVIR, COMBIVIR, EPZICOM, or TRIZIVIR. These drugs all contain lamivudine.

You should not take EPIVIR-HBV if you have had an allergic reaction to lamivudine.

EPIVIR-HBV has not been studied in children less than 2 years old.

Can pregnant women and nursing mothers take EPIVIR-HBV?

There are no studies of EPIVIR-HBV in pregnant women. If you are pregnant or if you become pregnant while taking EPIVIR-HBV, notify your doctor or healthcare provider immediately.

EPIVIR-HBV has not been shown to prevent the spread of the hepatitis B virus from mother to infant.

It is not known whether lamivudine is passed to the infant in breast milk. If there is lamivudine in the breast milk, this could cause side effects in nursing infants. Mothers should not breastfeed while taking EPIVIR-HBV or other forms of lamivudine.

How should I take EPIVIR-HBV?

Your doctor will tell you how much EPIVIR-HBV to take. The usual dose is 1 EPIVIR-HBV Tablet orally (by mouth) once a day. Your doctor may prescribe a lower dose if you have problems with your kidneys. EPIVIR-HBV may be taken with food or on an empty stomach. To help you remember to take your EPIVIR-HBV as prescribed, you should try to take EPIVIR-HBV at the same time each day. You must not skip doses or stop treatment without first talking with your doctor or healthcare provider. A strawberry-banana-flavored liquid of EPIVIR-HBV is available for patients who need a liquid.

If you miss your regular time for taking your dose, but then remember it during that same day, take your missed dose immediately. Then, take your next dose at the regularly scheduled time the following day. Do **not** take 2 doses of EPIVIR-HBV at once to make up for missing a dose.

If you are not sure what to do if you miss taking your medication, check with your doctor or healthcare provider for further instructions.

EPIVIR-HBV can usually be taken with many other medications; however, be sure to tell your doctor or healthcare provider about all medications (including over-the-counter and prescription drugs) that you are taking. EPIVIR-HBV Tablets and EPIVIR-HBV Oral Solution contain a lower dose of the same drug (lamivudine) as EPIVIR Tablets, EPIVIR Oral Solution, COMBIVIR Tablets, EPZICOM Tablets, and TRIZIVIR Tablets; therefore, EPIVIR-HBV should not be taken together with EPIVIR, COMBIVIR, EPZICOM, or TRIZIVIR.

You should talk to your doctor about any changes in your treatment.

What are the possible side effects of EPIVIR-HBV?

You should stay under the care of a doctor during treatment so you can be checked for possible serious side effects. Serious side effects such as inflammation of the pancreas can occur with EPIVIR-HBV. Lactic acid buildup in the body and an enlarged liver have been reported with EPIVIR-HBV; this is not common but can result in death.

Hepatitis B virus sometimes becomes resistant to EPIVIR-HBV during treatment, and some people have had tests showing that their hepatitis was getting worse around the time the virus became resistant. Some people also have worsening of hepatitis after stopping EPIVIR-HBV. You should discuss any change in treatment with your doctor.

In studies, the most common side effects seen during treatment with EPIVIR-HBV were ear, nose, and throat infections; malaise and fatigue (feeling tired and run down); headache; abdominal discomfort and pain; nausea and vomiting; diarrhea; muscle pain; sore throat; joint pain; fever or chills; and skin rash.

This list of possible side effects is not complete. Your doctor or pharmacist can discuss with you a more complete list of possible side effects with EPIVIR-HBV. Talk to your doctor right away about any side effects or other unusual symptoms that occur when taking EPIVIR-HBV.

Does EPIVIR-HBV reduce the risk of passing hepatitis B to others?

No, EPIVIR-HBV has not been shown to reduce the risk of passing hepatitis B to others through sexual contact or exposure to infected blood. EPIVIR-HBV also has not been shown to reduce the risk of a mother passing hepatitis B to her baby.

What previous or current medical problems or conditions should I discuss with my doctor or healthcare provider?

Talk to your doctor or healthcare provider if:

- You have HIV infection.
- You are pregnant or if you become pregnant while taking EPIVIR-HBV.
- You are breastfeeding.
- You have diabetes. Each 20-mL dose (100 mg) of EPIVIR-HBV Oral Solution contains 4 grams of sucrose.

Also talk to your doctor or healthcare provider about:

- Problems with your blood counts.
- Problems with your muscles.
- Problems with your kidneys.
- Problems with your pancreas.
- Any side effects or unusual symptoms during treatment.

How should I store EPIVIR-HBV Tablets and Oral Solution?

EPIVIR-HBV Tablets and Oral Solution should be stored at room temperature. They do not require refrigeration. **Keep EPIVIR-HBV and all medicines out of the reach of children.**

Other Information

This medication is prescribed for a particular condition. Do not use it for any other condition or give it to anybody else.

For more complete information about EPIVIR-HBV ask your doctor or pharmacist. You can also ask to read the longer information leaflet that is written for health professionals.

Keep EPIVIR-HBV and all medicines out of the reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

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