HIGHLIGHTS OF PRESCRIBING INFORMATION

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

EPIVIR-HBV (lamivudine) tablets for oral use
EPIVIR-HBV (lamivudine) oral solution
Initial U.S. Approval: 1995

WARNING: RISK OF LACTIC ACIDOSIS, EXACERBATIONS OF HEPATITIS B UPON DISCONTINUATION OF EPIVIR-HBV, AND RISK OF HIV-1 RESISTANCE IF EPIVIR-HBV IS USED IN PATIENTS WITH UNRECOGNIZED OR UNTREATED HIV-1 INFECTION

See full prescribing information for complete boxed warning

- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur. (5.1)**
- **Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti-hepatitis B therapy (including EPIVIR-HBV). Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.2)**
- **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-1 infection. HIV-1 resistance may emerge in chronic hepatitis B patients with unrecognized or untreated HIV-1 infection because the lamivudine dosage in EPIVIR-HBV is subtherapeutic and monotherapy is inappropriate for the treatment of HIV-1 infection. HIV counseling and testing should be offered to all patients before beginning treatment with EPIVIR-HBV and periodically during treatment. (5.3)**

----------INDICATIONS AND USAGE----------

- EPIVIR-HBV is a nucleoside analogue reverse transcriptase inhibitor indicated for the treatment of chronic hepatitis B virus infection associated with evidence of hepatitis B viral replication and active liver inflammation. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- Adult patients: 100 mg, once daily. (2.2)
- Pediatric patients aged 2 to 17 years: 3 mg per kg once daily up to 100 mg once daily. Prescribe oral solution for pediatric patients requiring less than 100 mg daily. (2.3)
- Patients with renal impairment: Doses of EPIVIR-HBV must be adjusted in accordance with renal function. (2.4)
- EPIVIR-HBV should not be used with other medications that contain lamivudine or emtricitabine. (2.5)

---------- DOSAGE FORMS AND STRENGTHS ----------

- Tablets: 100 mg (3)
- Oral Solution: 5 mg per mL (3)

----------CONTRAINDICATIONS----------

Patients with previously demonstrated clinically significant hypersensitivity (e.g., anaphylaxis) to any of the components of the products. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- EPIVIR-HBV should not be used with other medications that contain lamivudine or with medications that contain emtricitabine. (5.4)
- Emergence of Resistance-Associated HBV Substitutions: Monitor ALT and HBV DNA levels during lamivudine treatment to aid in treatment decisions if emergence of viral mutants or loss of therapeutic response is suspected. (2.6, 5.5)

---------- ADVERSE REACTIONS ----------

- The most common reported adverse reactions in those receiving EPIVIR-HBV (incidence greater than or equal to 10% and reported at a rate greater than placebo) were ear, nose and throat infections, sore throat, and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF LACTIC ACIDOSIS, EXACERBATIONS OF HEPATITIS B UPON DISCONTINUATION OF EPIVIR-HBV®, AND RISK OF HIV-1 RESISTANCE IF EPIVIR-HBV IS USED IN PATIENTS WITH UNRECOGNIZED OR UNTREATED HIV-1

Lactic Acidosis and Severe Hepatomegaly

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including EPIVIR-HBV. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur *[see Warnings and Precautions (5.1)]*.

Exacerbations of Hepatitis B Upon Discontinuation of EPIVIR-HBV

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 and Precautions (5.2)]*.

Risk of HIV-1 Resistance if EPIVIR-HBV Is Used in Patients With Unrecognized or Untreated HIV-1 Infection

EPIVIR-HBV is not approved for the treatment of HIV-1 infection because the lamivudine dosage in EPIVIR-HBV is subtherapeutic and monotherapy is inappropriate for the treatment of HIV-1 infection. HIV-1 resistance may emerge in chronic hepatitis B-infected patients with unrecognized or untreated HIV-1 infection. Counseling and testing should be offered to all patients before beginning treatment with EPIVIR-HBV and periodically during treatment *[see Warnings and Precautions (5.3)]*.

1 INDICATIONS AND USAGE

EPIVIR-HBV is indicated for the treatment of chronic hepatitis B virus (HBV) infection associated with evidence of hepatitis B viral replication and active liver inflammation *[see Clinical Studies (14.1, 14.2)]*.

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

- Due to high rates of resistance development in treated patients, initiation of treatment with EPIVIR-HBV should only be considered when the use of an alternative antiviral agent with a higher genetic barrier to resistance is not available or appropriate.
- EPIVIR-HBV has not been evaluated in patients co-infected with HIV, hepatitis C virus (HCV), or hepatitis delta virus.
- EPIVIR-HBV has not been evaluated in liver transplant recipients or in patients with chronic

hepatitis B virus infection with decompensated liver disease.

- EPIVIR-HBV has not been evaluated in pediatric patients younger than 2 years of age with chronic HBV infection.

2 DOSAGE AND ADMINISTRATION

2.1 HIV Counseling and Testing

HIV counseling and testing should be offered to all patients before beginning treatment with EPIVIR-HBV and periodically during treatment because of the risk of emergence of resistant-HIV-1 and limitation of treatment options if EPIVIR-HBV is prescribed to treat chronic hepatitis B infection in a patient who has unrecognized HIV-1 infection or acquires HIV-1 infection during treatment *[see Warnings and Precautions (5.3)]*.

2.2 Dosage in Adult Patients

The recommended oral dosage of EPIVIR-HBV is 100 mg once daily.

2.3 Dosage in Pediatric Patients

The recommended oral dosage of EPIVIR-HBV for pediatric patients aged 2 to 17 years is 3 mg per kg once daily up to a maximum daily dosage of 100 mg. The oral solution formulation should be prescribed for patients requiring a dosage less than 100 mg or if unable to swallow tablets.

2.4 Dosage Adjustment in Adult Patients With Renal Impairment

Dosage recommendations for adult patients with reduced renal function are provided in Table 1 *[see Clinical Pharmacology (12.3)]*.

Table 1. Dosage of EPIVIR-HBV in Adult Patients With Renal Impairment

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

Following correction of the dosage for renal impairment, no additional dosage modification of EPIVIR-HBV is required after routine (4-hour) hemodialysis or peritoneal dialysis *[see Clinical Pharmacology (12.3)]*.

There are insufficient data to recommend a specific dosage of EPIVIR-HBV in pediatric patients with renal impairment.

2.5 Important Administration Instructions

- EPIVIR-HBV tablets and oral solution may be administered with or without food.
- The tablets and oral solution may be used interchangeably *[see Clinical Pharmacology (12.3)]*.

- The oral solution should be used for doses less than 100 mg.
- EPIVIR-HBV should not be used with other medications that contain lamivudine or medications that contain emtricitabine *[see Warnings and Precautions (5.4)]*.

2.6 Assessing Patients During Treatment

Patients should be monitored regularly during treatment by a physician experienced in the management of chronic hepatitis B. 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.

3 DOSAGE FORMS AND STRENGTHS

- EPIVIR-HBV tablets: 100 mg, butterscotch-colored, film-coated, biconvex, capsule-shaped tablets imprinted with “GX CG5” on one side.
- EPIVIR-HBV oral solution: A clear, colorless to pale yellow, strawberry-banana–flavored liquid, containing 5 mg of lamivudine per 1 mL.

4 CONTRAINDICATIONS

EPIVIR-HBV is contraindicated in patients who have experienced a previous hypersensitivity reaction (e.g., anaphylaxis) to lamivudine or to any component of the tablets or oral solution.

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis and Severe Hepatomegaly With Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including EPIVIR-HBV 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-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-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).

5.2 Exacerbation of Hepatitis After Discontinuation of Treatment

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 4 for more information regarding frequency of posttreatment ALT elevations) *[see Adverse Reactions (6.1)]*. Although most events appear to have been self-limited, fatalities have been reported in some cases. The causal relationship of hepatitis exacerbation after discontinuation of EPIVIR-HBV has not been clearly established. Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment with EPIVIR-HBV. There is insufficient evidence to determine whether re-initiation of EPIVIR-HBV alters the course of posttreatment exacerbations of hepatitis.

5.3 Risk of HIV-1 Resistance if EPIVIR-HBV Is Used in Patients With Unrecognized or Untreated HIV-1 Infection

EPIVIR-HBV tablets and oral solution contain a lower lamivudine dose than the lamivudine dose in the following drugs used to treat HIV-1 infection:

- EPIVIR® tablets and oral solution,
- COMBIVIR® (lamivudine/zidovudine) tablets,
- EPZICOM® (abacavir sulfate and lamivudine) tablets, and
- TRIZIVIR® (abacavir, lamivudine, and zidovudine) tablets.

The formulation and dosage of lamivudine in EPIVIR-HBV are not approved for patients co-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-1 infection or acquires HIV-1 infection during treatment.

5.4 Coadministration With Other Medications Containing Lamivudine or Emtricitabine

Do not coadminister EPIVIR-HBV with other lamivudine-containing products including EPIVIR (lamivudine), COMBIVIR (lamivudine/zidovudine), EPZICOM (abacavir/lamivudine), or TRIZIVIR (abacavir/lamivudine/zidovudine).

Do not coadminister EPIVIR-HBV with emtricitabine-containing products including ATRIPLA® (efavirenz/emtricitabine/tenofovir disoproxil fumarate), COMPLERA® (rilpivirine/emtricitabine/tenofovir disoproxil fumarate), EMTRIVA® (emtricitabine), STRIBILD® (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate), or TRUVADA® (emtricitabine/tenofovir disoproxil fumarate).

5.5 Emergence of Resistance-Associated HBV Substitutions

In controlled clinical trials, YMDD-mutant HBV was detected in subjects with on–EPIVIR-HBV re-appearance of HBV DNA after an initial decline below the solution-hybridization assay limit *[see Microbiology (12.4)]*. Subjects treated with EPIVIR–

HBV (adults and children) with YMDD-mutant HBV at 52 weeks showed diminished treatment responses in comparison with subjects treated with EPIVIR–HBV without evidence of YMDD substitutions, including the following: lower rates of HBeAg seroconversion and HBeAg loss (no greater than placebo recipients), more frequent return of positive HBV DNA, and more frequent ALT elevations. In the controlled trials, when subjects 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 subjects with YMDD-mutant HBV, including subjects from the liver transplant setting and from other clinical trials. In clinical practice, monitoring of ALT and HBV DNA levels during treatment with EPIVIR-HBV may aid in treatment decisions if emergence of viral mutants is suspected.

6 ADVERSE REACTIONS

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

- Lactic acidosis and severe hepatomegaly with steatosis *[see Warnings and Precautions (5.1)]*.
- Exacerbation of hepatitis B after discontinuation of treatment *[see Warnings and Precautions (5.2)]*.
- Risk of emergence of resistant HIV-1 infection *[see Warnings and Precautions (5.3)]*.
- Risk of emergence of resistant HBV infection *[see Warnings and Precautions (5.4)]*.

6.1 Clinical Trials Experience

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

Adverse Reactions in Clinical Trials of Adults With Chronic Hepatitis B Virus Infection: Clinical adverse reactions (regardless of investigator's causality assessment) reported in greater or equal to 10% of subjects who received EPIVIR-HBV and reported at a rate greater than placebo are listed in Table 2.

Table 2. Clinical Adverse Reactions[a] Reported in ≥10% of Subjects who Received EPIVIR-HBV for 52 to 68 Weeks and at an Incidence Greater than Placebo (Trials 1-3)

Adverse Event	EPIVIR-HBV (n = 332)	Placebo (n = 200)
Ear, Nose, and Throat		
Ear, nose, and throat infections	25%	21%
Sore throat	13%	8%
Gastrointestinal		
Diarrhea	14%	12%

[a] Includes adverse events regardless of severity and causality assessment.

Specified laboratory abnormalities reported in subjects who received EPIVIR-HBV and reported at a rate greater than in subjects who received placebo are listed in Table 3.

Table 3. Frequencies of Specified Laboratory Abnormalities Reported During Treatment at a Greater Frequency in Subjects Treated with EPIVIR-HBV Than With Placebo (Trials 1-3)[a]

Test (Abnormal Level)	Subjects With Abnormality/Subjects With Observations	
	EPIVIR-HBV	Placebo
Serum Lipase ≥2.5 x ULN[b]	10%	7%
CPK ≥7 x baseline	9%	5%
Platelets <50,000/mm^3	4%	3%

[a] Includes subjects treated for 52 to 68 weeks.
[b] Includes observations during and after treatment in the 2 placebo-controlled trials that collected this information.
ULN = Upper limit of normal.

In subjects followed for up to 16 weeks after discontinuation of treatment, posttreatment ALT elevations were observed more frequently in subjects who had received EPIVIR-HBV than in subjects who had received placebo. A comparison of ALT elevations between Weeks 52 and 68 in subjects who discontinued EPIVIR-HBV at Week 52 and subjects in the same trials who received placebo throughout the treatment course is shown in Table 4.

Table 4. Posttreatment ALT Elevations With No-Active-Treatment Follow-up (Trials 1 and 3)

Abnormal Value	Subjects With ALT Elevation/ Subjects With Observations[a]	
	EPIVIR-HBV[b]	Placebo[b]
ALT ≥2 x baseline value	27%	19%
ALT ≥3 x baseline value[c]	21%	8%
ALT ≥2 x baseline value and absolute ALT >500 IU/L	15%	7%
ALT ≥2 x baseline value; and bilirubin >2 x ULN and ≥2 x baseline value	0.7%	0.9%

[a] Each subject may be represented in one or more category.
[b] During treatment phase.
[c] Comparable to a Grade 3 toxicity in accordance with modified WHO criteria.
ULN = Upper limit of normal.

Adverse Reactions in Clinical Trials of Pediatric Subjects With Chronic Hepatitis B Virus Infection: Most commonly observed adverse reactions in the pediatric trials were similar to those in adult trials. Posttreatment transaminase elevations were observed in some subjects followed after cessation of EPIVIR-HBV.

6.2 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been reported during postmarketing use of EPIVIR-HBV. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure. These reactions have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to lamivudine.

Blood and Lympatic System Disorders: Thrombocytopenia.

Digestive: Stomatitis.

Endocrine and Metabolic: Hyperglycemia.

General: Weakness.

Blood and Lymphatic: Anemia (including pure red cell aplasia and severe anemias progressing on therapy), lymphadenopathy, splenomegaly.

Hepatic and Pancreatic: Lactic acidosis and steatosis, posttreatment exacerbation of hepatitis *[see Boxed Warning]*, pancreatitis.

Hypersensitivity: Anaphylaxis, urticaria.

Musculoskeletal: Cramps, rhabdomyolysis.

Nervous: Paresthesia, peripheral neuropathy.

Respiratory: Abnormal breath sounds/wheezing.

Skin: Alopecia, pruritus, rash.

7 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). No data are available regarding interactions with other drugs that have renal clearance mechanisms similar to that of lamivudine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

There are no adequate and well-controlled trials of EPIVIR-HBV in pregnant women. Because animal reproduction studies are not always predictive of human response, EPIVIR-HBV should be used during pregnancy only if the potential benefits outweigh the potential risks to the fetus.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to lamivudine, a Pregnancy Registry has been established. Healthcare providers

are encouraged to register patients by calling 1-800-258-4263.

Animal Data: Animal reproduction studies in rats and rabbits revealed no evidence of teratogenicity. 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. Evidence of early embryolethality was seen in the rabbit at exposure levels similar to those observed in humans, but there was no indication of this effect in the rat at exposure levels up to 60 times those in humans.

Studies in pregnant rats and rabbits showed that lamivudine is transferred to the fetus through the placenta.

8.3 Nursing Mothers

Lamivudine is excreted in human milk. Samples of breast milk obtained from 20 mothers receiving lamivudine monotherapy (300 mg twice daily, 6 times the recommended dosage for hepatitis B infection) or combination therapy (150 mg lamivudine twice daily [3 times the recommended dosage for hepatitis B infection] and 300 mg zidovudine twice daily) had measurable concentrations of lamivudine.

Because of the potential for serious adverse reactions in nursing infants, a decision should be made to discontinue EPIVIR-HBV taking into consideration the importance of continued hepatitis B therapy to the mother and the known benefits of breastfeeding.

8.4 Pediatric Use

EPIVIR-HBV is indicated for the treatment of chronic hepatitis B virus infection in pediatric patients aged 2 to 17 years *[see Indications and Usage (1), Clinical Pharmacology (12.3), Clinical Studies (14.2)]*. The safety and efficacy of EPIVIR-HBV in pediatric patients younger than 2 years have not been established.

8.5 Geriatric Use

Clinical trials 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 Dosage and Administration (2.4), Clinical Pharmacology (12.3)]*.

8.6 Patients With Impaired Renal Function

Reduction of the dosage of EPIVIR-HBV is recommended for patients with impaired renal function *[see Dosage and Administration (2.4), Clinical Pharmacology (12.3)]*.

8.7 Patients With Impaired Liver Function

No dose adjustment for lamivudine is required for patients with impaired hepatic function.

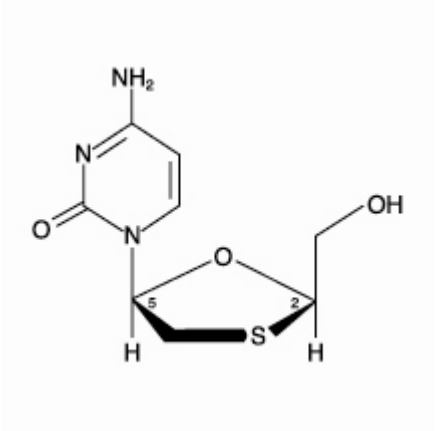
10 OVERDOSAGE

There is no known antidote for EPIVIR-HBV. If overdose occurs, the patient should be monitored, and standard supportive treatment utilized, as required.

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.

11 DESCRIPTION

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



Lamivudine is a white to off-white crystalline solid with a solubility of approximately 70 mg per 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 per 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).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lamivudine is an antiviral agent *[see Microbiology (12.4)]*.

12.3 Pharmacokinetics

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

Absorption and Bioavailability: 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 per mL and 1.05 ± 0.32 mcg per 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 mcg•hour per mL, respectively. The relative bioavailability of the tablet and oral solution were 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 oral solution and the tablet. Therefore, the oral 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.

Absolute bioavailability in 12 adult subjects was 86% ± 16% (mean ± SD) for the 150-mg tablet and 87% ± 13% for the 10-mg per mL oral solution.

Effects of Food on Oral Absorption: 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.

Distribution: The apparent volume of distribution after IV administration of lamivudine to 20 asymptomatic HIV-1-infected subjects was 1.3 ± 0.4 L per 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 less than 36% and independent of dose. In vitro studies showed that over the concentration range of 0.1 to 100 mcg per 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 humans, 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 per min (mean ± SD). In 20 HIV-1-infected subjects given a single IV dose, renal clearance was 280.4 ± 75.2 mL per min (mean ± SD), representing 71% ± 16% (mean ± SD) of total clearance of lamivudine.

In most single-dose trials in HIV-1-infected subjects, HBV-infected subjects, 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-1-infected subjects, total clearance was 398.5 ± 69.1 mL per min (mean ± SD). Oral clearance and elimination half-life were independent of dose and body weight over an oral dosing range of 0.25 to 10 mg per kg.

Special Populations: *Adults With Renal Impairment:* The pharmacokinetic properties of lamivudine have been determined in healthy subjects and in subjects with impaired renal function, with and without hemodialysis (Table 5).

Table 5. Pharmacokinetic Parameters (Mean ± SD) Dose-Normalized to a Single 100-mg Oral Dose of Lamivudine in Subjects 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•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 (2.4)]*.

Hemodialysis increases lamivudine clearance from a mean of 64 to 88 mL per 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.

Pediatric Patients With Renal Impairment: The effect of renal impairment on lamivudine pharmacokinetics in pediatric patients with chronic hepatitis B is not known.

Adults With Hepatic Impairment: The pharmacokinetic properties of lamivudine in adults with hepatic impairment are shown in Table 6). Subjects were stratified by severity of hepatic impairment.

Table 6. Pharmacokinetic Parameters (Mean ± SD) Dose-Normalized to a Single 100-mg Dose of Lamivudine in 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•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

[a] Hepatic impairment assessed by aminopyrine breath test.

Pharmacokinetic parameters were not altered by diminishing hepatic impairment. 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 Indications and Usage (1)]*.

Adults Post-Hepatic Transplant: Fourteen HBV-infected subjects 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 impairment; consequently, transplant patients with renal impairment had generally higher exposure than patients with normal renal function. Safety and efficacy of EPIVIR-HBV have not been established in this population *[see Indications and Usage (1)]*.

Pediatric Subjects: Lamivudine pharmacokinetics were evaluated in a 28-day dose-ranging trial in 53 pediatric subjects with chronic hepatitis B. Subjects aged 2 to 12 years were randomized to receive lamivudine 0.35 mg per kg twice daily, 3 mg per kg once daily, 1.5 mg per kg twice daily, or 4 mg per kg twice daily. Subjects aged 13 to 17 years received lamivudine 100 mg once daily. Lamivudine T_{max} was 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 per kg given once daily produced a steady-state lamivudine AUC (mean 5,953 ng•hour per mL ± 1,562 SD) similar to that associated with a dose of 100 mg per 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: *Interferon Alfa:* Multiple doses of lamivudine and a single dose of interferon were coadministered to 19 healthy male subjects in a pharmacokinetics trial. Results indicated a 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 trial.

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

Trimethoprim/Sulfamethoxazole: Lamivudine and trimethoprim/sulfamethoxazole (TMP/SMX) were coadministered to 14 HIV-positive subjects in a single-center, open-label, randomized, crossover trial. Each subject 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.

Zidovudine: Lamivudine and zidovudine were coadministered to 12 asymptomatic HIV-positive adult subjects in a single-center, open-label, randomized, crossover trial. 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.

12.4 Microbiology

Mechanism of Action: Lamivudine is a synthetic nucleoside analogue. Intracellularly, lamivudine is phosphorylated to its active 5′-triphosphate metabolite, lamivudine triphosphate, 3TC-TP. The principal mode of action of 3TC-TP is the inhibition of the RNA- and DNA-dependent polymerase activities of HBV reverse transcriptase (rt) via DNA chain termination after incorporation of the nucleotide analogue into viral DNA. 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 per mL) to 5.6 μM (1.3 mcg per mL) depending upon the duration of exposure of cells to lamivudine, the cell model system, and the protocol used. See the EPIVIR prescribing information for information regarding activity of lamivudine against HIV.

Resistance: Lamivudine-resistant isolates were identified in subjects 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 greater than 1 $\log_{10}$ (10-fold) increase in serum HBV DNA from nadir during treatment in a subject who had an initial virologic response.

Lamivudine-resistant HBV isolates develop rtM204V/I substitutions in the YMDD motif of the catalytic domain of the viral reverse transcriptase. rtM204V/I substitutions are frequently accompanied by other substitutions (rtV173L, rtL180M) which enhance the level of lamivudine resistance or act as compensatory substitutions improving replication efficiency. Other substitutions detected in lamivudine-resistant HBV isolates include rtL80I and rtA181T.

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 subjects receiving EPIVIR-HBV 100 mg once daily for 52 weeks. The prevalence of YMDD substitutions was less than 10% in each of these trials for subjects studied at 24 weeks and increased to an average of 24% (range in 4 trials: 16% to 32%) at 52 weeks. In limited data from a long-term follow-up trial in subjects who continued 100 mg per day EPIVIR-HBV after one of these trials, 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 subjects who developed YMDD-mutant HBV at any time was 69% (40 of 58).

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

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

Pediatric Subjects: In a controlled trial in pediatric subjects, YMDD-mutant HBV was detected in 31 of 166 (19%) subjects receiving EPIVIR-HBV for 52 weeks. For a subgroup that remained on therapy with EPIVIR-HBV in a follow-up trial, YMDD substitutions 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 treatment with EPIVIR-HBV.

Cross-Resistance: HBV containing lamivudine resistance-associated substitutions (rtL180M, rtM204I, rtM204V, rtL180M and rtM204V, rtV173L and rtL180M and rtM204V) retain susceptibility to adefovir dipivoxil but have reduced susceptibility to entecavir (30 fold) and telbivudine (greater than 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 greater than 1,000-fold reductions in susceptibility to lamivudine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Long-term carcinogenicity studies with lamivudine 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.

Mutagenesis: 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 per kg producing plasma levels of 60 to 70 times those in humans at the recommended dose for chronic hepatitis B.

Impairment of Fertility: In a study of reproductive performance, lamivudine administered to rats at doses up to 4,000 mg per 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.

14 CLINICAL STUDIES

14.1 Clinical Studies of EPIVIR-HBV in Adult Patients

The safety and efficacy of EPIVIR-HBV 100 mg once daily versus placebo were evaluated in 3 controlled trials in subjects with compensated chronic hepatitis B virus infection. All subjects were aged 16 years 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) and persistently elevated ALT levels and/or chronic inflammation on liver biopsy compatible with a diagnosis of chronic viral hepatitis. The results of these trials are summarized below.

- Trial 1 was a randomized, double-blind trial of EPIVIR-HBV 100 mg once daily versus placebo for 52 weeks followed by a 16-week no-treatment period in 141 treatment-naive US subjects.
- Trial 2 was a randomized, double-blind, 3-arm trial that compared EPIVIR-HBV 25 mg once daily versus EPIVIR-HBV 100 mg once daily versus placebo for 52 weeks in 358 Asian subjects.
- Trial 3 was a randomized, partially-blind trial conducted primarily in North America and Europe in 238 subjects who had ongoing evidence of active chronic hepatitis B despite previous treatment with interferon alfa. The trial 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).

Principal endpoint comparisons for the histologic and serologic outcomes in subjects receiving EPIVIR-HBV (100 mg daily) or placebo in these trials are shown in the following tables.

Table 7. Histologic Response at Week 52 Among Adult Subjects Receiving EPIVIR-HBV 100 mg Once Daily or Placebo

	Trial 1		Trial 2		Trial 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 greater than or equal to 2-point decrease in the Knodell Histologic Activity Index (HAI) at Week 52 compared with pretreatment HAI. Subjects with missing data at baseline were excluded.

Table 8. HBeAg Seroconverters[a] at Week 52 Among Adult Subjects Receiving EPIVIR-HBV 100 mg Once Daily or Placebo

	Trial 1		Trial 2		Trial 3	
Seroconversion	EPIVIR-HBV (n = 63)	Placebo (n = 69)	EPIVIR-HBV (n = 140)	Placebo (n = 70)	EPIVIR-HBV (n = 108)	Placebo (n = 53)
Seroconverters	17%	6%	16%	4%	15%	13%

[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 EPIVIR-HBV treatment compared with placebo in Trials 1-3.

The majority of subjects treated with EPIVIR–HBV 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 treatment with EPIVIR-HBV was observed in approximately one-third of subjects after this initial response.

14.2 Clinical Studies of EPIVIR-HBV in Pediatric Subjects

The safety and efficacy of EPIVIR-HBV were evaluated in a double-blind clinical trial in 286 subjects aged from 2 to 17 years, who were randomized (2:1) to receive 52 weeks of EPIVIR-HBV (3 mg per kg once daily to a maximum of 100 mg once daily) or placebo. All subjects 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 subjects treated with EPIVIR–HBV and 13% of placebo-treated subjects. Normalization of serum ALT was achieved and maintained to Week 52

more frequently in subjects treated with EPIVIR-HBV compared with placebo (55% versus 13%). As in the adult controlled trials, most subjects treated with EPIVIR–HBV 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 (aged 13 to 17 years) showed less evidence of treatment effect than younger pediatric subjects.

16 HOW SUPPLIED/STORAGE AND HANDLING

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.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Advice for the Patient

- Advise patients to remain under the care of a physician while taking EPIVIR-HBV and discuss any new symptoms or concurrent medications with their physician.
- Advise patients 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 *[see Dosage and Administration (2.6)]*.
- Inform patients that deterioration of liver disease has occurred in some cases when treatment was discontinued. Instruct patients to discuss any changes in regimen with their physician *[see Warnings and Precautions (5.2)]*.
- Inform patients 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 *[see Warnings and Precautions (5.5)]*.
- Counsel patients on the importance of testing for HIV to avoid inappropriate therapy and development of resistant HIV. HIV counseling and testing should be offered before starting EPIVIR-HBV and periodically during therapy.
- Advise patients 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 Dosage and Administration (2.1), Warnings and Precautions (5.3, 5.4)]*.

- Advise patients not to take EPIVIR-HBV with emtricitabine-containing medicines, such as ATRIPLA, COMPLERA, EMTRIVA, STRIBILD, or TRUVADA *[see Warnings and Precautions (5.4)]*.
- Advise patients 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 Use in Specific Populations (8.1)]*.
- Instruct patients to avoid doing things that can spread HBV infection to others.
  - **Do not share needles or other injection equipment.**
  - **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
  - **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- Advise diabetic patients that each 20-mL dose of EPIVIR-HBV oral solution contains 4 grams of sucrose *[see Description (11)]*.

GlaxoSmithKline
Research Triangle Park, NC 27709

Manufactured under agreement from
Shire Pharmaceuticals Group plc
Basingstoke, UK

EPH:PI

PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

PATIENT INFORMATION

EPIVIR-HBV® (EP-i-veer h-b-v)
(lamivudine)
tablets

EPIVIR-HBV® (EP-i-veer h-b-v)
(lamivudine)
oral solution

Read this Patient Information before you start taking EPIVIR-HBV and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is the most important information I should know about EPIVIR-HBV?

EPIVIR-HBV can cause serious side effects, including:

Build-up of an acid in your blood (lactic acidosis). Lactic acidosis can happen in some people who take EPIVIR-HBV or similar (nucleoside analogs) medicines. Lactic acidosis is a serious medical emergency that can lead to death.

Lactic acidosis can be hard to identify early because the symptoms could seem like symptoms of other health problems. **Call your healthcare provider right away if you get any of the following symptoms that could be signs of lactic acidosis:**

- feel very weak or tired
- unusual (not normal) muscle pain
- trouble breathing
- stomach pain with nausea and vomiting
- feel cold, especially in your arms and legs
- feel dizzy or light-headed
- have a fast or irregular heartbeat

Severe liver problems. Severe liver problems can happen in people who take EPIVIR-HBV or similar medicines. In some cases these liver problems can lead to death. Your liver may become large (hepatomegaly) and you may develop fat in your liver (steatosis) when you take EPIVIR-HBV. **Call your healthcare provider right away if you get any of the following signs of liver problems**:

- your skin or the white part of your eyes turns yellow (jaundice)
- dark “tea-colored” urine
- light-colored bowel movements (stools)
- loss of appetite for several days or longer
- nausea
- stomach pain

You may be more likely to get lactic acidosis or severe liver problems if you are female, very overweight, or have been taking nucleoside analogue medicines for a long time.

Worsening liver disease. Your hepatitis B infection may become worse after stopping treatment with EPIVIR-HBV. Worsening liver disease can be serious and may lead to death. If you stop treatment with EPIVIR-HBV, your healthcare provider will need to check your health and do blood tests to check your liver for at least several months after you stop taking EPIVIR-HBV.

Risk of HIV-1 resistance in people with unknown HIV-1 infection or in people with untreated HIV-1 infection. If you have or get HIV that is not being treated with medicines while taking EPIVIR-HBV, the HIV virus may develop resistance to certain HIV medicines and become harder to treat**.**

- Your healthcare provider should offer you counseling and testing for HIV-1 infection before you start treatment for hepatitis B with EPIVIR-HBV and during treatment.
- EPIVIR-HBV tablets and EPIVIR-HBV oral solution contain a lower dose of lamivudine than other medicines that contain lamivudine and are used to treat HIV-1 infection. See **“What should I tell my healthcare provider?”** for a list of medicines you should not take with EPIVIR-HBV.

Resistant Hepatitis B Virus (HBV). The hepatitis B virus can change (mutate) during your treatment with EPIVIR-HBV and become harder to treat (resistant). If this happens, your liver disease can become worse and may lead to death. Tell your healthcare provider right away if you have any new symptoms.

What is EPIVIR-HBV?

EPIVIR-HBV is a prescription medicine used to treat long-term (chronic) hepatitis B virus (HBV) when the disease is progressing and there is liver swelling (inflammation).

- EPIVIR-HBV will not cure HBV.
- EPIVIR-HBV may lower the amount of HBV in your body.

- EPIVIR-HBV may lower the ability of HBV to multiply and infect new liver cells.
- EPIVIR-HBV may improve the condition of your liver.
- The long-term benefits of taking EPIVIR-HBV for treatment of chronic hepatitis B infection are not known.

It is not known if EPIVIR-HBV is safe and effective in:

- people with chronic HBV who have a severely damaged liver that is unable to work properly (decompensated liver disease)
- people with hepatitis C virus or hepatitis D (delta) virus
- people who have had a liver transplant
- children with chronic HBV less than 2 years of age

EPIVIR-HBV does not stop you from spreading HBV to others by sex, sharing needles, or being exposed to your blood. Avoid doing things that can spread HBV infection to others.

- Do not share or re-use needles or other injection equipment.
- Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.
- Do not have any kind of sex without protection. Always practice safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.

A vaccine is available to protect people at risk for becoming infected with HBV. You can ask your healthcare provider for information about this vaccine.

Who should not take EPIVIR-HBV?

Do not take EPIVIR-HBV if you are allergic to lamivudine or any of the ingredients in EPIVIR-HBV. See the end of this leaflet for a complete list of ingredients in EPIVIR-HBV.

What should I tell my healthcare provider before taking EPIVIR-HBV?

Before you take EPIVIR-HBV, tell your healthcare provider if you:

- have HIV-1 infection
- have kidney problems
- have diabetes. Each 20-mL dose (100 mg) of EPIVIR-HBV oral solution contains 4 grams of sucrose.
- have any other medical condition
- are pregnant or plan to become pregnant. It is not known if EPIVIR-HBV will harm your unborn baby.

Pregnancy Registry. There is a pregnancy registry for women who take antiviral medicines during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry.

- are breastfeeding or plan to breastfeed. EPIVIR-HBV can pass into your breast milk and may harm your baby. You and your healthcare provider should decide if you will take EPIVIR-HBV or breastfeed.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Do not take EPIVIR-HBV if you also take:

- other medicines that contain lamivudine (COMBIVIR®, EPIVIR®, EPZICOM®, TRIZIVIR®)
- medicines that contain emtricitabine (ATRIPLA®, COMPLERA®, EMTRIVA®, STRIBILD®, TRUVADA®)

How should I take EPIVIR-HBV?

- Take EPIVIR-HBV exactly as your healthcare provider tells you to take it.
- Do not change your dose or stop taking EPIVIR-HBV without talking with your healthcare provider.
- EPIVIR-HBV is taken 1 time each day.
- Your healthcare provider may prescribe a lower dose if you have problems with your kidneys.
- For children 2 to 17 years of age, your healthcare provider will prescribe the right dose of EPIVIR-HBV based on your child's body weight.
- Take EPIVIR-HBV by mouth, with or without food.
- Tell your healthcare provider if you have trouble swallowing tablets. EPIVIR-HBV also comes as a liquid (oral solution).
- If you take too much EPIVIR-HBV, call your healthcare provider or go to the nearest hospital emergency room right away.
- It is important to stay under your healthcare provider's care while taking EPIVIR-HBV. Tell your healthcare provider about any new symptoms that you have.

What are the possible side effects of EPIVIR-HBV?

EPIVIR-HBV may cause serious side effects, including:

See **"What is the most important information I should know about EPIVIR-HBV?"**

The most common side effects of EPIVIR-HBV include:

- ear, nose, and throat infections
- sore throat
- diarrhea

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of EPIVIR-HBV. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store EPIVIR-HBV?

- Store EPIVIR-HBV tablets and oral solution at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep bottles of EPIVIR-HBV oral solution tightly closed.

Keep EPIVIR-HBV and all medicines out of the reach of children.

General information about the safe and effective use of EPIVIR-HBV

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use EPIVIR-HBV for a condition for which it was not prescribed. Do not give EPIVIR-HBV to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about EPIVIR-HBV that is written for health professionals.

For more information, go to www.gsk.com or call 1-888-825-5249.

What are the ingredients in EPIVIR-HBV?

Active ingredient: lamivudine
Inactive ingredients:
EPIVIR-HBV tablets: 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: artificial strawberry and banana flavors, citric acid (anhydrous), methylparaben, propylene glycol, propylparaben, sodium citrate (dihydrate), and sucrose (200 mg per mL).

This Patient Information has been approved by the U.S. Food and Drug Administration.

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