

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)

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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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

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1 **FULL PRESCRIBING INFORMATION**

2 **WARNING: RISK OF LACTIC ACIDOSIS, EXACERBATIONS OF HEPATITIS B**
3 **UPON DISCONTINUATION OF EPIVIR-HBV[®], AND RISK OF HIV-1 RESISTANCE IF**
4 **EPIVIR-HBV IS USED IN PATIENTS WITH UNRECOGNIZED OR UNTREATED HIV-1**
5

6 **Lactic Acidosis and Severe Hepatomegaly**

7 Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been
8 reported with the use of nucleoside analogues alone or in combination, including EPIVIR-
9 HBV. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or
10 pronounced hepatotoxicity occur [see *Warnings and Precautions (5.1)*].
11

12 **Exacerbations of Hepatitis B Upon Discontinuation of EPIVIR-HBV**

13 Severe acute exacerbations of hepatitis B have been reported in patients who have
14 discontinued anti-hepatitis B therapy (including EPIVIR-HBV). Hepatic function should
15 be monitored closely with both clinical and laboratory follow-up for at least several months
16 in patients who discontinue anti-hepatitis B therapy. If appropriate, initiation of
17 anti-hepatitis B therapy may be warranted [see *Warnings and Precautions (5.2)*].
18

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

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

27 **1 INDICATIONS AND USAGE**

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

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

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

- 38 hepatitis B virus infection with decompensated liver disease.
- 39 • EPIVIR-HBV has not been evaluated in pediatric patients younger than 2 years of age with
40 chronic HBV infection.

41 **2 DOSAGE AND ADMINISTRATION**

42 **2.1 HIV Counseling and Testing**

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

48 **2.2 Dosage in Adult Patients**

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

50 **2.3 Dosage in Pediatric Patients**

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

55 **2.4 Dosage Adjustment in Adult Patients With Renal Impairment**

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

58

59 **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

60

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

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

66 **2.5 Important Administration Instructions**

- 67 • EPIVIR-HBV tablets and oral solution may be administered with or without food.
- 68 • The tablets and oral solution may be used interchangeably [see *Clinical Pharmacology*
69 (12.3)].

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

73 **2.6 Assessing Patients During Treatment**

74 Patients should be monitored regularly during treatment by a physician experienced in the
75 management of chronic hepatitis B. During treatment, combinations of such events such as
76 return of persistently elevated ALT, increasing levels of HBV DNA over time after an initial
77 decline below assay limit, progression of clinical signs or symptoms of hepatic disease, and/or
78 worsening of hepatic necroinflammatory findings may be considered as potentially reflecting
79 loss of therapeutic response. Such observations should be taken into consideration when
80 determining the advisability of continuing therapy with EPIVIR-HBV.

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

84 **3 DOSAGE FORMS AND STRENGTHS**

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

89 **4 CONTRAINDICATIONS**

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

93 **5 WARNINGS AND PRECAUTIONS**

94 **5.1 Lactic Acidosis and Severe Hepatomegaly With Steatosis**

95 Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been
96 reported with the use of nucleoside analogues alone or in combination, including EPIVIR-HBV
97 and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged
98 nucleoside exposure may be risk factors. Most of these reports have described patients receiving
99 nucleoside analogues for treatment of HIV infection, but there have been reports of lactic
100 acidosis in patients receiving lamivudine for hepatitis B. Particular caution should be exercised
101 when administering EPIVIR-HBV to any patient with known risk factors for liver disease;
102 however, cases have also been reported in patients with no known risk factors. Treatment with
103 EPIVIR-HBV should be suspended in any patient who develops clinical or laboratory findings
104 suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and
105 steatosis even in the absence of marked transaminase elevations).

106 **5.2 Exacerbation of Hepatitis After Discontinuation of Treatment**

107 Clinical and laboratory evidence of exacerbations of hepatitis have occurred after

108 discontinuation of EPIVIR-HBV (these have been primarily detected by serum ALT elevations,
109 in addition to the re-emergence of HBV DNA commonly observed after stopping treatment; see
110 Table 4 for more information regarding frequency of posttreatment ALT elevations) [*see*
111 *Adverse Reactions (6.1)*]. Although most events appear to have been self-limited, fatalities have
112 been reported in some cases. The causal relationship of hepatitis exacerbation after
113 discontinuation of EPIVIR-HBV has not been clearly established. Patients should be closely
114 monitored with both clinical and laboratory follow-up for at least several months after stopping
115 treatment with EPIVIR-HBV. There is insufficient evidence to determine whether re-initiation of
116 EPIVIR-HBV alters the course of posttreatment exacerbations of hepatitis.

117 **5.3 Risk of HIV-1 Resistance if EPIVIR-HBV Is Used in Patients With** 118 **Unrecognized or Untreated HIV-1 Infection**

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

- 121 • EPIVIR[®] tablets and oral solution,
- 122 • COMBIVIR[®] (lamivudine/zidovudine) tablets,
- 123 • EPZICOM[®] (abacavir sulfate and lamivudine) tablets, and
- 124 • TRIZIVIR[®] (abacavir, lamivudine, and zidovudine) tablets.

125 The formulation and dosage of lamivudine in EPIVIR-HBV are not approved for patients
126 co-infected with HBV and HIV. If a decision is made to administer lamivudine to such patients,
127 the higher dosage indicated for HIV therapy should be used as part of an appropriate
128 combination regimen, and the prescribing information for EPIVIR, COMBIVIR, EPZICOM, or
129 TRIZIVIR, as well as for EPIVIR-HBV, should be consulted. HIV counseling and testing should
130 be offered to all patients before beginning EPIVIR-HBV and periodically during treatment
131 because of the risk of rapid emergence of resistant HIV and limitation of treatment options if
132 EPIVIR-HBV is prescribed to treat chronic hepatitis B in a patient who has unrecognized or
133 untreated HIV-1 infection or acquires HIV-1 infection during treatment.

134 **5.4 Coadministration With Other Medications Containing Lamivudine or** 135 **Emtricitabine**

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

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

144 **5.5 Emergence of Resistance-Associated HBV Substitutions**

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

148 HBV (adults and children) with YMDD-mutant HBV at 52 weeks showed diminished treatment
 149 responses in comparison with subjects treated with EPIVIR–HBV without evidence of YMDD
 150 substitutions, including the following: lower rates of HBeAg seroconversion and HBeAg loss (no
 151 greater than placebo recipients), more frequent return of positive HBV DNA, and more frequent
 152 ALT elevations. In the controlled trials, when subjects developed YMDD-mutant HBV, they had
 153 a rise in HBV DNA and ALT from their own previous on-treatment levels. Progression of
 154 hepatitis B, including death, has been reported in some subjects with YMDD-mutant HBV,
 155 including subjects from the liver transplant setting and from other clinical trials. In clinical
 156 practice, monitoring of ALT and HBV DNA levels during treatment with EPIVIR-HBV may aid
 157 in treatment decisions if emergence of viral mutants is suspected.

158 **6 ADVERSE REACTIONS**

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

- 161 • Lactic acidosis and severe hepatomegaly with steatosis [*see Warnings and Precautions*
 162 (5.1)].
- 163 • Exacerbation of hepatitis B after discontinuation of treatment [*see Warnings and Precautions*
 164 (5.2)].
- 165 • Risk of emergence of resistant HIV-1 infection [*see Warnings and Precautions* (5.3)].
- 166 • Risk of emergence of resistant HBV infection [*see Warnings and Precautions* (5.4)].

167 **6.1 Clinical Trials Experience**

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

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

175
 176 **Table 2. Clinical Adverse Reactions^a Reported in ≥10% of Subjects who Received EPIVIR-
 177 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%

178 ^a Includes adverse events regardless of severity and causality assessment.
 179

180 Specified laboratory abnormalities reported in subjects who received EPIVIR-HBV and
 181 reported at a rate greater than in subjects who received placebo are listed in Table 3.
 182

183 **Table 3. Frequencies of Specified Laboratory Abnormalities Reported During Treatment**
 184 **at a Greater Frequency in Subjects Treated with EPIVIR-HBV Than With Placebo (Trials**
 185 **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 $< 50,000/\text{mm}^3$	4%	3%

186 ^a Includes subjects treated for 52 to 68 weeks.

187 ^b Includes observations during and after treatment in the 2 placebo-controlled trials that collected
 188 this information.

189 ULN = Upper limit of normal.
 190

191 In subjects followed for up to 16 weeks after discontinuation of treatment, posttreatment
 192 ALT elevations were observed more frequently in subjects who had received EPIVIR-HBV than
 193 in subjects who had received placebo. A comparison of ALT elevations between Weeks 52 and
 194 68 in subjects who discontinued EPIVIR-HBV at Week 52 and subjects in the same trials who
 195 received placebo throughout the treatment course is shown in Table 4.
 196

197 **Table 4. Posttreatment ALT Elevations With No-Active-Treatment Follow-up (Trials 1**
 198 **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%

199 ^a Each subject may be represented in one or more category.

200 ^b During treatment phase.

201 ^c Comparable to a Grade 3 toxicity in accordance with modified WHO criteria.

202 ULN = Upper limit of normal.
 203

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

208 **6.2 Postmarketing Experience**

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

215 Blood and Lymphatic System Disorders: Thrombocytopenia.

216 Digestive: Stomatitis.

217 Endocrine and Metabolic: Hyperglycemia.

218 General: Weakness.

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

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

223 Hypersensitivity: Anaphylaxis, urticaria.

224 Musculoskeletal: Cramps, rhabdomyolysis.

225 Nervous: Paresthesia, peripheral neuropathy.

226 Respiratory: Abnormal breath sounds/wheezing.

227 Skin: Alopecia, pruritus, rash.

228 **7 DRUG INTERACTIONS**

229 Lamivudine is predominantly eliminated in the urine by active organic cationic secretion.
230 The possibility of interactions with other drugs administered concurrently should be considered,
231 particularly when their main route of elimination is active renal secretion via the organic cationic
232 transport system (e.g., trimethoprim). No data are available regarding interactions with other
233 drugs that have renal clearance mechanisms similar to that of lamivudine.

234 **8 USE IN SPECIFIC POPULATIONS**

235 **8.1 Pregnancy**

236 *Pregnancy Category C.*

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

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

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

244 **Animal Data:** Animal reproduction studies in rats and rabbits revealed no evidence of
245 teratogenicity. Reproduction studies have been performed in rats and rabbits at orally
246 administered doses up to 4,000 mg/kg/day and 1,000 mg/kg/day, respectively, producing plasma
247 levels up to approximately 60 times that for the adult HBV dose. Evidence of early
248 embryoletality was seen in the rabbit at exposure levels similar to those observed in humans,
249 but there was no indication of this effect in the rat at exposure levels up to 60 times those in
250 humans.

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

253 **8.3 Nursing Mothers**

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

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

262 **8.4 Pediatric Use**

263 EPIVIR-HBV is indicated for the treatment of chronic hepatitis B virus infection in
264 pediatric patients aged 2 to 17 years [*see Indications and Usage (1), Clinical Pharmacology*
265 *(12.3), Clinical Studies (14.2)*]. The safety and efficacy of EPIVIR-HBV in pediatric patients
266 younger than 2 years have not been established.

267 **8.5 Geriatric Use**

268 Clinical trials of EPIVIR-HBV did not include sufficient numbers of subjects aged 65
269 and over to determine whether they respond differently from younger subjects. In general, dose
270 selection for an elderly patient should be cautious, reflecting the greater frequency of decreased
271 hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. In
272 particular, because lamivudine is substantially excreted by the kidney and elderly patients are
273 more likely to have decreased renal function, renal function should be monitored and dosage
274 adjustments should be made accordingly [*see Dosage and Administration (2.4), Clinical*
275 *Pharmacology (12.3)*].

276 **8.6 Patients With Impaired Renal Function**

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

279 **8.7 Patients With Impaired Liver Function**

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

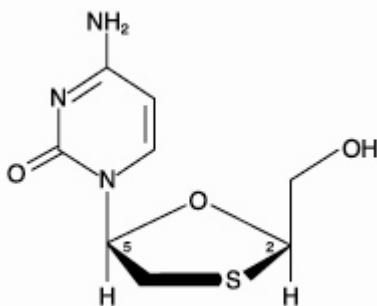
282 **10 OVERDOSAGE**

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

285 Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis,
286 continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if
287 continuous hemodialysis would provide clinical benefit in a lamivudine overdose event.

288 **11 DESCRIPTION**

289 EPIVIR-HBV is a synthetic nucleoside analogue with activity against HBV. The
290 chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-
291 (1H)-pyrimidin-2-one. Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine.
292 Lamivudine has also been referred to as (-)2',3'-dideoxy, 3'-thiacytidine. It has a molecular
293 formula of C₈H₁₁N₃O₃S and a molecular weight of 229.3. It has the following structural formula:



294
295
296 Lamivudine is a white to off-white crystalline solid with a solubility of approximately
297 70 mg per mL in water at 20°C.

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

302 EPIVIR-HBV oral solution is for oral administration. One milliliter (1 mL) of
303 EPIVIR-HBV oral solution contains 5 mg of lamivudine (5 mg per mL) in an aqueous solution
304 and the inactive ingredients artificial strawberry and banana flavors, citric acid (anhydrous),
305 methylparaben, propylene glycol, propylparaben, sodium citrate (dihydrate), and sucrose
306 (200 mg).

307 **12 CLINICAL PHARMACOLOGY**

308 **12.1 Mechanism of Action**

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

310 **12.3 Pharmacokinetics**

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

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

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

326 Absolute bioavailability in 12 adult subjects was $86\% \pm 16\%$ (mean \pm SD) for the
327 150-mg tablet and $87\% \pm 13\%$ for the 10-mg per mL oral solution.

328 *Effects of Food on Oral Absorption:* The 100-mg tablet was administered orally to
329 24 healthy subjects on 2 occasions, once in the fasted state and once with food (standard meal:
330 967 kcal; 67 grams fat, 33 grams protein, 58 grams carbohydrate). There was no significant
331 difference in systemic exposure (AUC) in the fed and fasted states.

332 *Distribution:* The apparent volume of distribution after IV administration of
333 lamivudine to 20 asymptomatic HIV-1-infected subjects was 1.3 ± 0.4 L per kg, suggesting that
334 lamivudine distributes into extravascular spaces. Volume of distribution was independent of dose
335 and did not correlate with body weight.

336 Binding of lamivudine to human plasma proteins is less than 36% and independent of
337 dose. In vitro studies showed that over the concentration range of 0.1 to 100 mcg per mL, the
338 amount of lamivudine associated with erythrocytes ranged from 53% to 57% and was
339 independent of concentration.

340 *Metabolism:* Metabolism of lamivudine is a minor route of elimination. In humans,
341 the only known metabolite of lamivudine is the trans-sulfoxide metabolite. In 9 healthy subjects
342 receiving 300 mg of lamivudine as single oral doses, a total of 4.2% (range: 1.5% to 7.5%) of the
343 dose was excreted as the trans-sulfoxide metabolite in the urine, the majority of which was
344 excreted in the first 12 hours. Serum concentrations of the trans-sulfoxide metabolite have not
345 been determined.

346 *Elimination:* The majority of lamivudine is eliminated unchanged in urine by active
347 organic cationic secretion. In 9 healthy subjects given a single 300-mg oral dose of lamivudine,
348 renal clearance was 199.7 ± 56.9 mL per min (mean \pm SD). In 20 HIV-1-infected subjects given
349 a single IV dose, renal clearance was 280.4 ± 75.2 mL per min (mean \pm SD), representing
350 $71\% \pm 16\%$ (mean \pm SD) of total clearance of lamivudine.

351 In most single-dose trials in HIV-1-infected subjects, HBV-infected subjects, or healthy
 352 subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life
 353 ($t_{1/2}$) ranged from 5 to 7 hours. In HIV-1-infected subjects, total clearance was 398.5 ± 69.1 mL
 354 per min (mean \pm SD). Oral clearance and elimination half-life were independent of dose and
 355 body weight over an oral dosing range of 0.25 to 10 mg per kg.

356 **Special Populations: Adults With Renal Impairment:** The pharmacokinetic properties
 357 of lamivudine have been determined in healthy subjects and in subjects with impaired renal
 358 function, with and without hemodialysis (Table 5).
 359

360 **Table 5. Pharmacokinetic Parameters (Mean \pm SD) Dose-Normalized to a Single 100-mg**
 361 **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

362
 363 Exposure (AUC), C_{max} , and half-life increased with diminishing renal function (as
 364 expressed by creatinine clearance). Apparent total oral clearance (Cl/F) of lamivudine decreased
 365 as creatinine clearance decreased. T_{max} was not significantly affected by renal function. Based on
 366 these observations, it is recommended that the dosage of lamivudine be modified in patients with
 367 renal impairment [see Dosage and Administration (2.4)].

368 Hemodialysis increases lamivudine clearance from a mean of 64 to 88 mL per min;
 369 however, the length of time of hemodialysis (4 hours) was insufficient to significantly alter mean
 370 lamivudine exposure after a single-dose administration. Continuous ambulatory peritoneal
 371 dialysis and automated peritoneal dialysis have negligible effects on lamivudine clearance.
 372 Therefore, it is recommended, following correction of dose for creatinine clearance, that no
 373 additional dose modification be made after routine hemodialysis or peritoneal dialysis.

374 It is not known whether lamivudine can be removed by continuous (24-hour)
 375 hemodialysis.

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

378 **Adults With Hepatic Impairment:** The pharmacokinetic properties of lamivudine in
 379 adults with hepatic impairment are shown in Table 6). Subjects were stratified by severity of
 380 hepatic impairment.
 381

382 **Table 6. Pharmacokinetic Parameters (Mean ± SD) Dose-Normalized to a Single 100-mg**
 383 **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
Cl _r (mL/min)	279.2 ± 79.2	323.5 ± 100.9	216.1 ± 58.0

384 ^a Hepatic impairment assessed by aminopyrine breath test.

385
 386 Pharmacokinetic parameters were not altered by diminishing hepatic impairment.
 387 Therefore, no dose adjustment for lamivudine is required for patients with impaired hepatic
 388 function. Safety and efficacy of EPIVIR-HBV have not been established in the presence of
 389 decompensated liver disease [*see Indications and Usage (1)*].

390 **Adults Post-Hepatic Transplant:** Fourteen HBV-infected subjects received liver
 391 transplant following lamivudine therapy and completed pharmacokinetic assessments at
 392 enrollment, 2 weeks after 100-mg once-daily dosing (pre-transplant), and 3 months following
 393 transplant; there were no significant differences in pharmacokinetic parameters. The overall
 394 exposure of lamivudine is primarily affected by renal impairment; consequently, transplant
 395 patients with renal impairment had generally higher exposure than patients with normal renal
 396 function. Safety and efficacy of EPIVIR-HBV have not been established in this population [*see*
 397 *Indications and Usage (1)*].

398 **Pediatric Subjects:** Lamivudine pharmacokinetics were evaluated in a 28-day
 399 dose-ranging trial in 53 pediatric subjects with chronic hepatitis B. Subjects aged 2 to 12 years
 400 were randomized to receive lamivudine 0.35 mg per kg twice daily, 3 mg per kg once daily,
 401 1.5 mg per kg twice daily, or 4 mg per kg twice daily. Subjects aged 13 to 17 years received
 402 lamivudine 100 mg once daily. Lamivudine T_{max} was 0.5 to 1 hour. In general, both C_{max} and
 403 exposure (AUC) showed dose proportionality in the dosing range studied. Weight-corrected oral
 404 clearance was highest at age 2 and declined from 2 to 12 years, where values were then similar to
 405 those seen in adults. A dose of 3 mg per kg given once daily produced a steady-state lamivudine
 406 AUC (mean 5,953 ng•hour per mL ± 1,562 SD) similar to that associated with a dose of 100 mg
 407 per day in adults.

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

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

410 **Drug Interactions: Interferon Alfa:** Multiple doses of lamivudine and a single dose of
 411 interferon were coadministered to 19 healthy male subjects in a pharmacokinetics trial. Results
 412 indicated a 10% reduction in lamivudine AUC, but no change in interferon pharmacokinetic
 413 parameters when the 2 drugs were given in combination. All other pharmacokinetic parameters

414 (C_{\max} , T_{\max} , and $t_{1/2}$) were unchanged. There was no significant pharmacokinetic interaction
415 between lamivudine and interferon alfa in this trial.

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

422 **Trimethoprim/Sulfamethoxazole:** Lamivudine and trimethoprim/sulfamethoxazole
423 (TMP/SMX) were coadministered to 14 HIV-positive subjects in a single-center, open-label,
424 randomized, crossover trial. Each subject received treatment with a single 300-mg dose of
425 lamivudine and TMP 160 mg/SMX 800 mg once a day for 5 days with concomitant
426 administration of lamivudine 300 mg with the fifth dose in a crossover design. Coadministration
427 of TMP/SMX with lamivudine resulted in an increase of $44\% \pm 23\%$ (mean \pm SD) in lamivudine
428 AUC, a decrease of $29\% \pm 13\%$ in lamivudine oral clearance, and a decrease of $30\% \pm 36\%$ in
429 lamivudine renal clearance. The pharmacokinetic properties of TMP and SMX were not altered
430 by coadministration with lamivudine.

431 **Zidovudine:** Lamivudine and zidovudine were coadministered to 12 asymptomatic
432 HIV-positive adult subjects in a single-center, open-label, randomized, crossover trial. No
433 significant differences were observed in AUC or total clearance for lamivudine or zidovudine
434 when the 2 drugs were administered together. Coadministration of lamivudine with zidovudine
435 resulted in an increase of $39\% \pm 62\%$ (mean \pm SD) in C_{\max} of zidovudine.

436 **12.4 Microbiology**

437 **Mechanism of Action:** Lamivudine is a synthetic nucleoside analogue. Intracellularly,
438 lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate,
439 3TC-TP. The principal mode of action of 3TC-TP is the inhibition of the RNA- and DNA-
440 dependent polymerase activities of HBV reverse transcriptase (rt) via DNA chain termination
441 after incorporation of the nucleotide analogue into viral DNA. 3TC-TP is a weak inhibitor of
442 mammalian α , β , and γ -DNA polymerases.

443 **Antiviral Activity:** Activity of lamivudine against HBV in cell culture was assessed in
444 HBV DNA-transfected 2.2.15 cells, HB611 cells, and infected human primary hepatocytes. EC_{50}
445 values (the concentration of drug needed to reduce the level of extracellular HBV DNA by 50%)
446 varied from 0.01 μ M (2.3 ng per mL) to 5.6 μ M (1.3 mcg per mL) depending upon the duration
447 of exposure of cells to lamivudine, the cell model system, and the protocol used. See the EPIVIR
448 prescribing information for information regarding activity of lamivudine against HIV.

449 **Resistance:** Lamivudine-resistant isolates were identified in subjects with virologic
450 breakthrough, defined when using solution hybridization assay as the detection of HBV DNA in
451 serum on 2 or more occasions after failing to detect HBV DNA on 2 or more occasions and
452 defined when using PCR assay as a greater than 1 \log_{10} (10-fold) increase in serum HBV DNA
453 from nadir during treatment in a subject who had an initial virologic response.

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

459 In 4 controlled clinical trials in adults with HBeAg-positive chronic hepatitis B virus
460 infection (CHB), YMDD-mutant HBV was detected in 81 of 335 subjects receiving EPIVIR-
461 HBV 100 mg once daily for 52 weeks. The prevalence of YMDD substitutions was less than
462 10% in each of these trials for subjects studied at 24 weeks and increased to an average of 24%
463 (range in 4 trials: 16% to 32%) at 52 weeks. In limited data from a long-term follow-up trial in
464 subjects who continued 100 mg per day EPIVIR-HBV after one of these trials, YMDD
465 substitutions further increased from 18% (10 of 57) at 1 year to 41% (20 of 49), 53% (27 of 51),
466 and 69% (31 of 45) after 2, 3, and 4 years of treatment, respectively. Over the 5-year treatment
467 period, the proportion of subjects who developed YMDD-mutant HBV at any time was 69% (40
468 of 58).

469 In a controlled trial, treatment-naive subjects with HBeAg-positive CHB were treated
470 with EPIVIR-HBV or EPIVIR-HBV plus adefovir dipivoxil combination therapy. Following
471 104 weeks of therapy, YMDD-mutant HBV was detected in 7 of 40 (18%) subjects receiving
472 combination therapy compared with 15 of 35 (43%) subjects receiving therapy with only
473 EPIVIR-HBV. In another controlled trial, combination therapy was evaluated in adult subjects
474 with HBeAg-positive CHB who had YMDD-mutant HBV and diminished clinical and virologic
475 response to EPIVIR-HBV. Following 52 weeks of EPIVIR-HBV plus adefovir dipivoxil
476 combination therapy (n = 46) or therapy with only EPIVIR-HBV (n = 49), YMDD-mutant HBV
477 was detected less frequently in subjects receiving combination therapy, 62% versus 96%.

478 A published trial suggested that the rates of lamivudine resistance in subjects treated for
479 HBeAg-negative CHB appear to be more variable (0% to 27% at 1 year and 10% to 56% at
480 2 years).

481 *Pediatric Subjects:* In a controlled trial in pediatric subjects, YMDD-mutant HBV
482 was detected in 31 of 166 (19%) subjects receiving EPIVIR-HBV for 52 weeks. For a subgroup
483 that remained on therapy with EPIVIR-HBV in a follow-up trial, YMDD substitutions increased
484 from 24% (29 of 121) at 12 months to 59% (68 of 115) at 24 months and 64% (66 of 103) at
485 36 months of treatment with EPIVIR-HBV.

486 Cross-Resistance: HBV containing lamivudine resistance-associated substitutions
487 (rtL180M, rtM204I, rtM204V, rtL180M and rtM204V, rtV173L and rtL180M and rtM204V)
488 retain susceptibility to adefovir dipivoxil but have reduced susceptibility to entecavir (30 fold)
489 and telbivudine (greater than 100 fold). The lamivudine resistance-associated substitution
490 rtA181T results in diminished response to adefovir and telbivudine. Similarly, HBV with
491 entecavir resistance-associated substitutions (I169T/M250V and T184G/S202I) have greater than
492 1,000-fold reductions in susceptibility to lamivudine.

493 **13 NONCLINICAL TOXICOLOGY**

494 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

495 Carcinogenesis: Long-term carcinogenicity studies with lamivudine in mice and rats
496 showed no evidence of carcinogenic potential at exposures up to 34 times (mice) and 200 times
497 (rats) those observed in humans at the recommended therapeutic dose for chronic hepatitis B.

498 Mutagenesis: Lamivudine was not active in a microbial mutagenicity screen or an in
499 vitro cell transformation assay, but showed weak in vitro mutagenic activity in a cytogenetic
500 assay using cultured human lymphocytes and in the mouse lymphoma assay. However,
501 lamivudine showed no evidence of in vivo genotoxic activity in the rat at oral doses of up to
502 2,000 mg per kg producing plasma levels of 60 to 70 times those in humans at the recommended
503 dose for chronic hepatitis B.

504 Impairment of Fertility: In a study of reproductive performance, lamivudine
505 administered to rats at doses up to 4,000 mg per kg per day, producing plasma levels 80 to 120
506 times those in humans, revealed no evidence of impaired fertility and no effect on the survival,
507 growth, and development to weaning of the offspring.

508 **14 CLINICAL STUDIES**

509 **14.1 Clinical Studies of EPIVIR-HBV in Adult Patients**

510 The safety and efficacy of EPIVIR-HBV 100 mg once daily versus placebo were
511 evaluated in 3 controlled trials in subjects with compensated chronic hepatitis B virus infection.
512 All subjects were aged 16 years or older and had chronic hepatitis B virus infection (serum
513 HBsAg-positive for at least 6 months) accompanied by evidence of HBV replication (serum
514 HBeAg-positive and positive for serum HBV DNA) and persistently elevated ALT levels and/or
515 chronic inflammation on liver biopsy compatible with a diagnosis of chronic viral hepatitis. The
516 results of these trials are summarized below.

- 517 • Trial 1 was a randomized, double-blind trial of EPIVIR-HBV 100 mg once daily versus
518 placebo for 52 weeks followed by a 16-week no-treatment period in 141 treatment-naive US
519 subjects.
- 520 • Trial 2 was a randomized, double-blind, 3-arm trial that compared EPIVIR-HBV 25 mg once
521 daily versus EPIVIR-HBV 100 mg once daily versus placebo for 52 weeks in 358 Asian
522 subjects.
- 523 • Trial 3 was a randomized, partially-blind trial conducted primarily in North America and
524 Europe in 238 subjects who had ongoing evidence of active chronic hepatitis B despite
525 previous treatment with interferon alfa. The trial compared EPIVIR-HBV 100 mg once daily
526 for 52 weeks, followed by either EPIVIR-HBV 100 mg or matching placebo once daily for
527 16 weeks (Arm 1), versus placebo once daily for 68 weeks (Arm 2).

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

531

532 **Table 7. Histologic Response at Week 52 Among Adult Subjects Receiving EPIVIR-HBV**
 533 **100 mg Once Daily or Placebo**

Assessment	Trial 1		Trial 2		Trial 3	
	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%

534 ^a Improvement was defined as a greater than or equal to 2-point decrease in the Knodell
 535 Histologic Activity Index (HAI) at Week 52 compared with pretreatment HAI. Subjects with
 536 missing data at baseline were excluded.

537
 538 **Table 8. HBeAg Seroconverters^a at Week 52 Among Adult Subjects Receiving**
 539 **EPIVIR-HBV 100 mg Once Daily or Placebo**

Seroconversion	Trial 1		Trial 2		Trial 3	
	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%

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

543
 544 Normalization of serum ALT levels was more frequent with EPIVIR-HBV treatment
 545 compared with placebo in Trials 1-3.

546 The majority of subjects treated with EPIVIR-HBV showed a decrease of HBV DNA to
 547 below the assay limit early in the course of therapy. However, reappearance of assay-detectable
 548 HBV DNA during treatment with EPIVIR-HBV was observed in approximately one-third of
 549 subjects after this initial response.

550 **14.2 Clinical Studies of EPIVIR-HBV in Pediatric Subjects**

551 The safety and efficacy of EPIVIR-HBV were evaluated in a double-blind clinical trial in
 552 286 subjects aged from 2 to 17 years, who were randomized (2:1) to receive 52 weeks of
 553 EPIVIR-HBV (3 mg per kg once daily to a maximum of 100 mg once daily) or placebo. All
 554 subjects had compensated chronic hepatitis B accompanied by evidence of hepatitis B virus
 555 replication (positive serum HBeAg and positive for serum HBV DNA by a research
 556 branched-chain DNA assay) and persistently elevated serum ALT levels. The combination of
 557 loss of HBeAg and reduction of HBV DNA to below the assay limit of the research assay,
 558 evaluated at Week 52, was observed in 23% of subjects treated with EPIVIR-HBV and 13% of
 559 placebo-treated subjects. Normalization of serum ALT was achieved and maintained to Week 52

560 more frequently in subjects treated with EPIVIR-HBV compared with placebo (55% versus
561 13%). As in the adult controlled trials, most subjects treated with EPIVIR-HBV had decreases in
562 HBV DNA below the assay limit early in treatment, but about one-third of subjects with this
563 initial response had reappearance of assay-detectable HBV DNA during treatment. Adolescents
564 (aged 13 to 17 years) showed less evidence of treatment effect than younger pediatric subjects.

565 **16 HOW SUPPLIED/STORAGE AND HANDLING**

566 EPIVIR-HBV tablets, 100 mg, are butterscotch-colored, film-coated, biconvex,
567 capsule-shaped tablets imprinted with “GX CG5” on one side.

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

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

571
572 EPIVIR-HBV oral solution, a clear, colorless to pale yellow, strawberry-banana-flavored
573 liquid, contains 5 mg of lamivudine in each 1 mL in plastic bottles of 240 mL.

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

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

578 **17 PATIENT COUNSELING INFORMATION**

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

580 Advice for the Patient

- 581 • Advise patients to remain under the care of a physician while taking EPIVIR-HBV and
582 discuss any new symptoms or concurrent medications with their physician.
- 583 • Advise patients that EPIVIR-HBV is not a cure for hepatitis B, that the long-term treatment
584 benefits of EPIVIR-HBV are unknown at this time, and, in particular, that the relationship of
585 initial treatment response to outcomes such as hepatocellular carcinoma and decompensated
586 cirrhosis is unknown [see *Dosage and Administration (2.6)*].
- 587 • Inform patients that deterioration of liver disease has occurred in some cases when treatment
588 was discontinued. Instruct patients to discuss any changes in regimen with their physician
589 [see *Warnings and Precautions (5.2)*].
- 590 • Inform patients that emergence of resistant hepatitis B virus and worsening of disease can
591 occur during treatment, and they should promptly report any new symptoms to their
592 physician [see *Warnings and Precautions (5.5)*].
- 593 • Counsel patients on the importance of testing for HIV to avoid inappropriate therapy and
594 development of resistant HIV. HIV counseling and testing should be offered before starting
595 EPIVIR-HBV and periodically during therapy.
- 596 • Advise patients that EPIVIR-HBV tablets and EPIVIR-HBV oral solution contain a lower
597 dose of the same active ingredient (lamivudine) as EPIVIR tablets, EPIVIR oral solution,
598 COMBIVIR tablets, EPZICOM tablets, and TRIZIVIR tablets. EPIVIR-HBV should not be

- 599 taken concurrently with EPIVIR, COMBIVIR, EPZICOM, or TRIZIVIR [see Dosage and
600 Administration (2.1), Warnings and Precautions (5.3, 5.4)].
- 601 • Advise patients not to take EPIVIR-HBV with emtricitabine-containing medicines, such as
602 ATRIPLA, COMPLERA, EMTRIVA, STRIBILD, or TRUVADA [see Warnings and
603 Precautions (5.4)].
 - 604 • Advise patients that treatment with EPIVIR-HBV has not been shown to reduce the risk of
605 transmission of HBV to others through sexual contact or blood contamination [see Use in
606 Specific Populations (8.1)].
 - 607 • Instruct patients to avoid doing things that can spread HBV infection to others.
 - 608 • **Do not share needles or other injection equipment.**
 - 609 • **Do not share personal items that can have blood or body fluids on them, like**
610 **toothbrushes and razor blades.**
 - 611 • **Do not have any kind of sex without protection.** Always practice safe sex by using a
612 latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal
613 secretions, or blood.
 - 614 • Advise diabetic patients that each 20-mL dose of EPIVIR-HBV oral solution contains
615 4 grams of sucrose [see Description (11)].
- 616

617 EPIVIR-HBV is a registered trademark of the GlaxoSmithKline group of companies.

618
619 EPIVIR, COMBIVIR, EPZICOM, and TRIZIVIR are registered trademarks of the ViiV
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627 GlaxoSmithKline
628 Research Triangle Park, NC 27709

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630 Manufactured under agreement from
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632 Basingstoke, UK

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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:**

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

682

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

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

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

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

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

706 **What is EPIVIR-HBV?**

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

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

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

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

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

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

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

732

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

735 **Who should not take EPIVIR-HBV?**

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

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

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

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

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

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

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

757 **Do not take EPIVIR-HBV if you also take:**

- 758 • other medicines that contain lamivudine (COMBIVIR[®], EPIVIR[®], EPZICOM[®],
759 TRIZIVIR[®])
- 760 • medicines that contain emtricitabine (ATRIPLA[®], COMPLERA[®], EMTRIVA[®],
761 STRIBILD[®], TRUVADA[®])

762 **How should I take EPIVIR-HBV?**

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

779 **What are the possible side effects of EPIVIR-HBV?**

780 **EPIVIR-HBV may cause serious side effects, including:**

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

783 **The most common side effects of EPIVIR-HBV include:**

- 784 • ear, nose, and throat infections
- 785 • sore throat
- 786 • diarrhea

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

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

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

793 **How should I store EPIVIR-HBV?**

- 794 • Store EPIVIR-HBV tablets and oral solution at room temperature between
795 68°F to 77°F (20°C to 25°C).
- 796 • Keep bottles of EPIVIR-HBV oral solution tightly closed.

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

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

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

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

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

807

808 **What are the ingredients in EPIVIR-HBV?**

809 **Active ingredient:** lamivudine

810 **Inactive ingredients:**

811 **EPIVIR-HBV tablets:** hypromellose, macrogol 400, magnesium stearate,
812 microcrystalline cellulose, polysorbate 80, red iron oxide, sodium starch glycolate,
813 titanium dioxide, and yellow iron oxide.

814 **EPIVIR-HBV oral solution:** artificial strawberry and banana flavors, citric acid
815 (anhydrous), methylparaben, propylene glycol, propylparaben, sodium citrate
816 (dihydrate), and sucrose (200 mg per mL).

817

818 This Patient Information has been approved by the U.S. Food and Drug
819 Administration.
820
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