

1 **PRESCRIBING INFORMATION**

2 **EPIVIR-HBV[®]**

3 **(lamivudine)**

4 **Tablets**

5
6 **EPIVIR-HBV[®]**

7 **(lamivudine)**

8 **Oral Solution**

9
10 **WARNING**

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

15 **HUMAN IMMUNODEFICIENCY VIRUS (HIV) COUNSELING AND TESTING**
16 **SHOULD BE OFFERED TO ALL PATIENTS BEFORE BEGINNING EPIVIR-HBV**
17 **AND PERIODICALLY DURING TREATMENT (SEE WARNINGS), BECAUSE**
18 **EPIVIR-HBV TABLETS AND ORAL SOLUTION CONTAIN A LOWER DOSE OF THE**
19 **SAME ACTIVE INGREDIENT (LAMIVUDINE) AS EPIVIR[®] TABLETS AND ORAL**
20 **SOLUTION USED TO TREAT HIV INFECTION. IF TREATMENT WITH**
21 **EPIVIR-HBV IS PRESCRIBED FOR CHRONIC HEPATITIS B FOR A PATIENT**
22 **WITH UNRECOGNIZED OR UNTREATED HIV INFECTION, RAPID EMERGENCE**
23 **OF HIV RESISTANCE IS LIKELY BECAUSE OF SUBTHERAPEUTIC DOSE AND**
24 **INAPPROPRIATE MONOTHERAPY.**

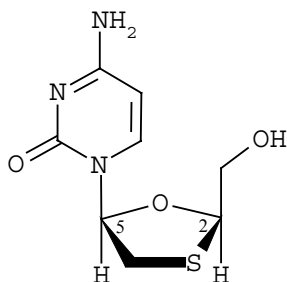
25
26 **DESCRIPTION**

27 **EPIVIR-HBV is a brand name for lamivudine, a synthetic nucleoside analogue with activity**
28 **against HBV and HIV. Lamivudine was initially developed for the treatment of HIV infection as**

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

29 EPIVIR[®]. Please see the complete prescribing information for EPIVIR Tablets and Oral Solution
30 for additional information. The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-
31 hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)-enantiomer of a
32 dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)-2',3'-dideoxy, 3'-
33 thiacytidine. It has a molecular formula of C₈H₁₁N₃O₃S and a molecular weight of 229.3. It has
34 the following structural formula:

35



36

37

38 Lamivudine is a white to off-white crystalline solid with a solubility of approximately
39 70 mg/mL in water at 20°C.

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

44 **EPIVIR-HBV Oral Solution** is for oral administration. One milliliter (1 mL) of
45 EPIVIR-HBV Oral Solution contains 5 mg of lamivudine (5 mg/mL) in an aqueous solution and
46 the inactive ingredients artificial strawberry and banana flavors, citric acid (anhydrous),
47 methylparaben, propylene glycol, propylparaben, sodium citrate (dihydrate), and sucrose
48 (200 mg).

49

50 **MICROBIOLOGY**

51 **Mechanism of Action:** Lamivudine is a synthetic nucleoside analogue. Lamivudine is
52 phosphorylated intracellularly to lamivudine triphosphate, L-TP. Incorporation of the
53 monophosphate form into viral DNA by hepatitis B virus (HBV) polymerase results in DNA
54 chain termination. L-TP also inhibits the RNA- and DNA-dependent DNA polymerase activities

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

55 of HIV-1 reverse transcriptase (RT). L-TP is a weak inhibitor of mammalian alpha-, beta-, and
56 gamma-DNA polymerases.

57 **Antiviral Activity In Vitro:** In vitro activity of lamivudine against HBV was assessed in HBV
58 DNA-transfected 2.2.15 cells, HB611 cells, and infected human primary hepatocytes. IC₅₀ values
59 (the concentration of drug needed to reduce the level of extracellular HBV DNA by 50%) varied
60 from 0.01 μM (2.3 ng/mL) to 5.6 μM (1.3 mcg/mL) depending upon the duration of exposure of
61 cells to lamivudine, the cell model system, and the protocol used. See the EPIVIR package insert
62 for information regarding activity of lamivudine against HIV.

63 **Drug Resistance: HBV:** Genotypic analysis of viral isolates obtained from patients who show
64 renewed evidence of replication of HBV while receiving lamivudine suggests that a reduction in
65 sensitivity of HBV to lamivudine is associated with mutations resulting in a methionine to valine
66 or isoleucine substitution in the YMDD motif of the catalytic domain of HBV polymerase
67 (position 552) and a leucine to methionine substitution at position 528. It is not known whether
68 other HBV mutations may be associated with reduced lamivudine susceptibility in vitro.

69 In 4 controlled clinical trials in adults, YMDD-mutant HBV were detected in 81 of
70 335 patients receiving lamivudine 100 mg once daily for 52 weeks. The prevalence of YMDD
71 mutations was less than 10% in each of these trials for patients studied at 24 weeks and increased
72 to an average of 24% (range in 4 studies: 16% to 32%) at 52 weeks. In limited data from a
73 long-term follow-up trial in patients who continued 100 mg/day lamivudine after one of these
74 studies, YMDD mutations further increased from 16% at 1 year to 42% at 2 years. In small
75 numbers of patients receiving lamivudine for longer periods, further increases in the appearance
76 of YMDD mutations were observed.

77 In a controlled trial in pediatric patients, YMDD-mutant HBV were detected in 31 of 166
78 (19%) patients receiving lamivudine for 52 weeks. For a subgroup who remained on lamivudine
79 therapy in a follow-up study, YMDD mutations increased from 24% at 12 months to 45% (53 of
80 118) at 18 months of lamivudine treatment.

81 Mutant viruses were associated with evidence of diminished treatment response at 52 weeks
82 relative to lamivudine-treated patients without evidence of YMDD mutations in both adult and
83 pediatric studies (see PRECAUTIONS). The long-term clinical significance of YMDD-mutant
84 HBV is not known.

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

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

88

89 **CLINICAL PHARMACOLOGY**

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

93 The pharmacokinetic properties of lamivudine have also been studied in asymptomatic,
94 HIV-infected adult patients after administration of single intravenous (IV) doses ranging from
95 0.25 to 8 mg/kg, as well as single and multiple (twice-daily regimen) oral doses ranging from
96 0.25 to 10 mg/kg.

97 **Absorption and Bioavailability:** Lamivudine was rapidly absorbed after oral
98 administration in HBV-infected patients and in healthy subjects. Following single oral doses of
99 100 mg, the peak serum lamivudine concentration (C_{max}) in HBV-infected patients (steady state)
100 and healthy subjects (single dose) was 1.28 ± 0.56 mcg/mL and 1.05 ± 0.32 mcg/mL
101 (mean \pm SD), respectively, which occurred between 0.5 and 2 hours after administration. The
102 area under the plasma concentration versus time curve ($AUC_{[0-24 \text{ hr}]}$) following 100 mg
103 lamivudine oral single and repeated daily doses to steady state was 4.3 ± 1.4 (mean \pm SD) and
104 4.7 ± 1.7 mcg•hr/mL, respectively. The relative bioavailability of the tablet and solution were
105 then demonstrated in healthy subjects. Although the solution demonstrated a slightly higher peak
106 serum concentration (C_{max}), there was no significant difference in systemic exposure (AUC_{∞})
107 between the solution and the tablet. Therefore, the solution and the tablet may be used
108 interchangeably.

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

112 The 100-mg tablet was administered orally to 24 healthy subjects on 2 occasions, once in the
113 fasted state and once with food (standard meal: 967 kcal; 67 grams fat, 33 grams protein,
114 58 grams carbohydrate). There was no significant difference in systemic exposure (AUC_{∞}) in the

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

115 fed and fasted states; therefore, EPIVIR-HBV Tablets and Oral Solution may be administered
116 with or without food.

117 Lamivudine was rapidly absorbed after oral administration in HIV-infected patients. Absolute
118 bioavailability in 12 adult patients was $86\% \pm 16\%$ (mean \pm SD) for the 150-mg tablet and
119 $87\% \pm 13\%$ for the 10-mg/mL oral solution.

120 ***Distribution:*** The apparent volume of distribution after IV administration of lamivudine to
121 20 asymptomatic HIV-infected patients was 1.3 ± 0.4 L/kg, suggesting that lamivudine
122 distributes into extravascular spaces. Volume of distribution was independent of dose and did not
123 correlate with body weight.

124 Binding of lamivudine to human plasma proteins is low ($<36\%$) and independent of dose. In
125 vitro studies showed that, over the concentration range of 0.1 to 100 mcg/mL, the amount of
126 lamivudine associated with erythrocytes ranged from 53% to 57% and was independent of
127 concentration.

128 ***Metabolism:*** Metabolism of lamivudine is a minor route of elimination. In man, the only
129 known metabolite of lamivudine is the trans-sulfoxide metabolite. In 9 healthy subjects receiving
130 300 mg of lamivudine as single oral doses, a total of 4.2% (range 1.5% to 7.5%) of the dose was
131 excreted as the trans-sulfoxide metabolite in the urine, the majority of which was excreted in the
132 first 12 hours.

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

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

139 In most single-dose studies in HIV- or HBV-infected patients or healthy subjects with serum
140 sampling for 24 hours after dosing, the observed mean elimination half-life ($t_{1/2}$) ranged from 5 to
141 7 hours. In HIV-infected patients, total clearance was 398.5 ± 69.1 mL/min (mean \pm SD). Oral
142 clearance and elimination half-life were independent of dose and body weight over an oral dosing
143 range from 0.25 to 10 mg/kg.

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

144 **Special Populations: Adults With Impaired Renal Function:** The pharmacokinetic
145 properties of lamivudine have been determined in healthy subjects and in subjects with impaired
146 renal function, with and without hemodialysis (Table 1):

147

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

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

150

151 Exposure (AUC_∞), C_{max}, and half-life increased with diminishing renal function (as expressed
152 by creatinine clearance). Apparent total oral clearance (Cl/F) of lamivudine decreased as
153 creatinine clearance decreased. T_{max} was not significantly affected by renal function. Based on
154 these observations, it is recommended that the dosage of lamivudine be modified in patients with
155 renal impairment (see DOSAGE AND ADMINISTRATION).

156 Hemodialysis increases lamivudine clearance from a mean of 64 to 88 mL/min; however, the
157 length of time of hemodialysis (4 hours) was insufficient to significantly alter mean lamivudine
158 exposure after a single-dose administration. Therefore, it is recommended, following correction
159 of dose for creatinine clearance, that no additional dose modification is made after routine
160 hemodialysis.

161 It is not known whether lamivudine can be removed by peritoneal dialysis or continuous
162 (24-hour) hemodialysis.

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

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

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

168

169 **Table 2. Pharmacokinetic Parameters (Mean ± SD) Dose-Normalized to a Single 100-mg**
170 **Dose of Lamivudine in 3 Groups of Subjects With Normal or Impaired Hepatic Function**

Parameter	Normal (n = 8)	Impairment*	
		Moderate (n = 8)	Severe (n = 8)
C _{max} (mcg/mL)	0.92 ± 0.31	1.06 ± 0.58	1.08 ± 0.27
AUC _∞ (mcg•hr/mL)	3.96 ± 0.58	3.97 ± 1.36	4.30 ± 0.63
T _{max} (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

171 *Hepatic impairment assessed by aminopyrine breath test.

172

173 Pharmacokinetic parameters were not altered by diminishing hepatic function. Therefore, no
174 dose adjustment for lamivudine is required for patients with impaired hepatic function. Safety
175 and efficacy of EPIVIR-HBV have not been established in the presence of decompensated liver
176 disease (see PRECAUTIONS).

177 **Post-Hepatic Transplant:** Fourteen HBV-infected patients received liver transplant
178 following lamivudine therapy and completed pharmacokinetic assessments at enrollment,
179 2 weeks after 100-mg once-daily dosing (pre-transplant), and 3 months following transplant;
180 there were no significant differences in pharmacokinetic parameters. The overall exposure of
181 lamivudine is primarily affected by renal dysfunction; consequently, transplant patients with
182 reduced renal function had generally higher exposure than patients with normal renal function.
183 Safety and efficacy of EPIVIR-HBV have not been established in this population (see
184 PRECAUTIONS).

185 **Pediatric Patients:** Lamivudine pharmacokinetics were evaluated in a 28-day dose-ranging
186 study in 53 pediatric patients with chronic hepatitis B. Patients aged 2 to 12 years were

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

187 randomized to receive lamivudine 0.35 mg/kg twice daily, 3 mg/kg once daily, 1.5 mg/kg twice
188 daily, or 4 mg/kg twice daily. Patients aged 13 to 17 years received lamivudine 100 mg once
189 daily. Lamivudine was rapidly absorbed (T_{max} 0.5 to 1 hour). In general, both C_{max} and exposure
190 (AUC) showed dose proportionality in the dosing range studied. Weight-corrected oral clearance
191 was highest at age 2 and declined from 2 to 12 years, where values were then similar to those
192 seen in adults. A dose of 3 mg/kg given once daily produced a steady-state lamivudine AUC
193 (mean 5953 ng•hr/mL \pm 1,562 SD) similar to that associated with a dose of 100 mg/day in adults.

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

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

196 **Drug Interactions:** Multiple doses of lamivudine and a single dose of interferon were
197 coadministered to 19 healthy male subjects in a pharmacokinetics study. Results indicated a
198 small (10%) reduction in lamivudine AUC, but no change in interferon pharmacokinetic
199 parameters when the 2 drugs were given in combination. All other pharmacokinetic parameters
200 (C_{max} , T_{max} , and $t_{1/2}$) were unchanged. There was no significant pharmacokinetic interaction
201 between lamivudine and interferon alfa in this study.

202 Lamivudine and zidovudine were coadministered to 12 asymptomatic HIV-positive adult
203 patients in a single-center, open-label, randomized, crossover study. No significant differences
204 were observed in AUC_{∞} or total clearance for lamivudine or zidovudine when the 2 drugs were
205 administered together. Coadministration of lamivudine with zidovudine resulted in an increase of
206 39% \pm 62% (mean \pm SD) in C_{max} of zidovudine.

207 Lamivudine and trimethoprim/sulfamethoxazole (TMP/SMX) were coadministered to 14
208 HIV-positive patients in a single-center, open-label, randomized, crossover study. Each patient
209 received treatment with a single 300-mg dose of lamivudine and TMP 160 mg/SMX 800 mg
210 once a day for 5 days with concomitant administration of lamivudine 300 mg with the fifth dose
211 in a crossover design. Coadministration of TMP/SMX with lamivudine resulted in an increase of
212 44% \pm 23% (mean \pm SD) in lamivudine AUC_{∞} , a decrease of 29% \pm 13% in lamivudine oral
213 clearance, and a decrease of 30% \pm 36% in lamivudine renal clearance. The pharmacokinetic
214 properties of TMP and SMX were not altered by coadministration with lamivudine (see
215 PRECAUTIONS: Drug Interactions).

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

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

218

219 **INDICATIONS AND USAGE**

220 EPIVIR-HBV is indicated for the treatment of chronic hepatitis B associated with evidence of
221 hepatitis B viral replication and active liver inflammation. This indication is based on 1-year
222 histologic and serologic responses in adult patients with compensated chronic hepatitis B, and
223 more limited information from a study in pediatric patients ages 2 to 17 years (see Description of
224 Clinical Studies below).

225 **Description of Clinical Studies: Adults:** The safety and efficacy of EPIVIR-HBV were
226 evaluated in 4 controlled studies in 967 patients with compensated chronic hepatitis B. All
227 patients were 16 years of age or older and had chronic hepatitis B virus infection (serum HBsAg
228 positive for at least 6 months) accompanied by evidence of HBV replication (serum HBeAg
229 positive and positive for serum HBV DNA, as measured by a research solution-hybridization
230 assay) and persistently elevated ALT levels and/or chronic inflammation on liver biopsy
231 compatible with a diagnosis of chronic viral hepatitis. Three of these studies provided
232 comparisons of EPIVIR-HBV 100 mg once daily versus placebo, and results of these
233 comparisons are summarized below.

- 234 • Study 1 was a randomized, double-blind study of EPIVIR-HBV 100 mg once daily versus
235 placebo for 52 weeks, followed by a 16-week no-treatment period, in treatment-naive US
236 patients.
- 237 • Study 2 was a randomized, double-blind, 3-arm study that compared EPIVIR-HBV 25 mg
238 once daily versus EPIVIR-HBV 100 mg once daily versus placebo for 52 weeks in Asian
239 patients.
- 240 • Study 3 was a randomized, partially-blind, 3-arm study conducted primarily in North America
241 and Europe in patients who had ongoing evidence of active chronic hepatitis B despite
242 previous treatment with interferon alfa. The study compared EPIVIR-HBV 100 mg once
243 daily for 52 weeks, followed by either EPIVIR-HBV 100 mg or matching placebo once daily
244 for 16 weeks (Arm 1), versus placebo once daily for 68 weeks (Arm 2). (A third arm using a

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

245 combination of interferon and lamivudine is not presented here because there was not
246 sufficient information to evaluate this regimen.)

247 Principal endpoint comparisons for the histologic and serologic outcomes in lamivudine
248 (100 mg daily) and placebo recipients in placebo-controlled studies are shown in the following
249 tables.

250

251 **Table 3. Histologic Response at Week 52 Among Adult Patients Receiving EPIVIR-HBV**
252 **100 mg Once Daily or Placebo**

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

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

256

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

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

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

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

263

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

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

270 **Pediatrics:** The safety and efficacy of EPIVIR-HBV were evaluated in a double-blind
271 clinical trial in 286 patients ranging from 2 to 17 years of age, who were randomized (2:1) to
272 receive 52 weeks of lamivudine (3 mg/kg once daily to a maximum of 100 mg once daily) or
273 placebo. All patients had compensated chronic hepatitis B accompanied by evidence of hepatitis
274 B virus replication (positive serum HBeAg and positive for serum HBV DNA by a research
275 branched-chain DNA assay) and persistently elevated serum ALT levels. The combination of loss
276 of HBeAg and reduction of HBV DNA to below the assay limit of the research assay, evaluated
277 at Week 52, was observed in 23% of lamivudine subjects and 13% of placebo subjects.
278 Normalization of serum ALT was achieved and maintained to Week 52 more frequently in
279 patients treated with EPIVIR-HBV compared with placebo (55% versus 13%). As in the adult
280 controlled trials, most lamivudine-treated subjects had decreases in HBV DNA below the assay

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

281 limit early in treatment, but about one third of subjects with this initial response had
282 reappearance of assay-detectable HBV DNA during treatment. Adolescents (ages 13 to 17 years)
283 showed less evidence of treatment effect than younger children.

284

285 **CONTRAINDICATIONS**

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

289

290 **WARNINGS**

291 **Lactic Acidosis/Severe Hepatomegaly with Steatosis:** Lactic acidosis and severe
292 hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside
293 analogues alone or in combination, including lamivudine and other antiretrovirals. A majority of
294 these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors.
295 Most of these reports have described patients receiving nucleoside analogues for treatment of
296 HIV infection, but there have been reports of lactic acidosis in patients receiving lamivudine for
297 hepatitis B. Particular caution should be exercised when administering EPIVIR or EPIVIR-HBV
298 to any patient with known risk factors for liver disease; however, cases have also been reported
299 in patients with no known risk factors. Treatment with EPIVIR or EPIVIR-HBV should be
300 suspended in any patient who develops clinical or laboratory findings suggestive of lactic
301 acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in
302 the absence of marked transaminase elevations).

303 **Important Differences Between Lamivudine-Containing Products, HIV Testing,**
304 **and Risk of Emergence of Resistant HIV:** EPIVIR-HBV Tablets and Oral Solution contain
305 a lower dose of the same active ingredient (lamivudine) as EPIVIR Tablets and Oral Solution,
306 COMBIVIR[®] (lamivudine/zidovudine) Tablets, and TRIZIVIR[®] (abacavir, lamivudine, and
307 zidovudine) Tablets used to treat HIV infection. The formulation and dosage of lamivudine in
308 EPIVIR-HBV are not appropriate for patients dually infected with HBV and HIV. If a decision is
309 made to administer lamivudine to such patients, the higher dosage indicated for HIV therapy
310 should be used as part of an appropriate combination regimen, and the prescribing information

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

311 for EPIVIR , COMBIVIR, or TRIZIVIR as well as for EPIVIR-HBV should be consulted. HIV
312 counseling and testing should be offered to all patients before beginning EPIVIR-HBV and
313 periodically during treatment because of the risk of rapid emergence of resistant HIV and
314 limitation of treatment options if EPIVIR-HBV is prescribed to treat chronic hepatitis B in a
315 patient who has unrecognized or untreated HIV infection or acquires HIV infection during
316 treatment.

317 **Posttreatment Exacerbations of Hepatitis:** Clinical and laboratory evidence of
318 exacerbations of hepatitis have occurred after discontinuation of EPIVIR-HBV (these have been
319 primarily detected by serum ALT elevations, in addition to the re-emergence of HBV DNA
320 commonly observed after stopping treatment; see Table 7 for more information regarding
321 frequency of posttreatment ALT elevations). Although most events appear to have been
322 self-limited, fatalities have been reported in some cases. The causal relationship to
323 discontinuation of lamivudine treatment is unknown. Patients should be closely monitored with
324 both clinical and laboratory follow-up for at least several months after stopping treatment. There
325 is insufficient evidence to determine whether re-initiation of therapy alters the course of
326 posttreatment exacerbations of hepatitis.

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

329

330 **PRECAUTIONS**

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

333 **Emergence of Resistance-Associated HBV Mutations:** In controlled clinical trials,
334 YMDD-mutant HBV were detected in patients with on-lamivudine re-appearance of HBV DNA
335 after an initial decline below the solution hybridization assay limit (see MICROBIOLOGY: Drug
336 Resistance). These mutations can be detected by a research assay and have been associated with
337 reduced susceptibility to lamivudine in vitro. Lamivudine-treated patients (adult and pediatric)
338 with YMDD-mutant HBV at 52 weeks showed diminished treatment responses in comparison to
339 lamivudine-treated patients without evidence of YMDD mutations, including lower rates of
340 HBeAg seroconversion and HBeAg loss (no greater than placebo recipients), more frequent

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

341 return of positive HBV DNA by solution hybridization or branched-chain DNA assay, and more
342 frequent ALT elevations. In the controlled trials, when patients developed YMDD-mutant HBV,
343 they had a rise in HBV DNA and ALT from their own previous on-treatment levels. Progression
344 of hepatitis B, including death, has been reported in some patients with YMDD-mutant HBV,
345 including patients from the liver transplant setting and from other clinical trials. The long-term
346 clinical significance of YMDD-mutant HBV is not known. Increased clinical and laboratory
347 monitoring may aid in treatment decisions if emergence of viral mutants is suspected.

348 **Limitations of Populations Studied:** Safety and efficacy of EPIVIR-HBV have not been
349 established in patients with decompensated liver disease or organ transplants; pediatric patients
350 <2 years of age; patients dually infected with HBV and HCV, hepatitis delta, or HIV; or other
351 populations not included in the principal phase III controlled studies. There are no studies in
352 pregnant women and no data regarding effect on vertical transmission, and appropriate infant
353 immunizations should be used to prevent neonatal acquisition of HBV.

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

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

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

369 **Information for Patients:** A Patient Package Insert (PPI) for EPIVIR-HBV is available for
370 patient information.

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

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

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

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

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

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

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

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

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

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

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

407 **Carcinogenesis, Mutagenesis, and Impairment of Fertility:** Lamivudine long-term
408 carcinogenicity studies in mice and rats showed no evidence of carcinogenic potential at
409 exposures up to 34 times (mice) and 200 times (rats) those observed in humans at the
410 recommended therapeutic dose for chronic hepatitis B. Lamivudine was not active in a microbial
411 mutagenicity screen or an in vitro cell transformation assay, but showed weak in vitro mutagenic
412 activity in a cytogenetic assay using cultured human lymphocytes and in the mouse lymphoma
413 assay. However, lamivudine showed no evidence of in vivo genotoxic activity in the rat at oral
414 doses of up to 2,000 mg/kg producing plasma levels of 60 to 70 times those in humans at the
415 recommended dose for chronic hepatitis B. In a study of reproductive performance, lamivudine
416 administered to rats at doses up to 4,000 mg/kg/day, producing plasma levels 80 to 120 times
417 those in humans, revealed no evidence of impaired fertility and no effect on the survival, growth,
418 and development to weaning of the offspring.

419 **Pregnancy:** Pregnancy Category C. Reproduction studies have been performed in rats and
420 rabbits at orally administered doses up to 4,000 mg/kg/day and 1,000 mg/kg/day, respectively,
421 producing plasma levels up to approximately 60 times that for the adult HBV dose. No evidence
422 of teratogenicity due to lamivudine was observed. Evidence of early embryoletality was seen in
423 the rabbit at exposure levels similar to those observed in humans, but there was no indication of
424 this effect in the rat at exposures up to 60 times that in humans. Studies in pregnant rats and
425 rabbits showed that lamivudine is transferred to the fetus through the placenta. There are no
426 adequate and well-controlled studies in pregnant women. Because animal reproductive toxicity
427 studies are not always predictive of human response, lamivudine should be used during
428 pregnancy only if the potential benefits outweigh the risks.

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

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

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

434 **Nursing Mothers:** A study in lactating rats showed that lamivudine concentrations in milk
435 were similar to those in plasma. Lamivudine is also excreted in human milk. Samples of breast
436 milk obtained from 20 mothers receiving lamivudine monotherapy (300 mg twice daily) or
437 combination therapy (150 mg lamivudine twice daily and 300 mg zidovudine twice daily) had
438 measurable concentrations of lamivudine.

439 Because of both the potential for HIV transmission and the potential for serious adverse
440 reactions in nursing infants, **mothers should be instructed not to breastfeed if they are**
441 **receiving lamivudine.**

442 **Pediatric Use: HBV:** Safety and efficacy of lamivudine for treatment of chronic hepatitis B in
443 children have been studied in pediatric patients from 2 to 17 years of age in a controlled clinical
444 trial (see CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, and DOSAGE AND
445 ADMINISTRATION).

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

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

449 **Geriatric Use:** Clinical studies of EPIVIR-HBV did not include sufficient numbers of subjects
450 aged 65 and over to determine whether they respond differently from younger subjects. In
451 general, dose selection for an elderly patient should be cautious, reflecting the greater frequency
452 of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.
453 In particular, because lamivudine is substantially excreted by the kidney and elderly patients are
454 more likely to have decreased renal function, renal function should be monitored and dosage
455 adjustments should be made accordingly (see PRECAUTIONS: Patients with Impaired Renal
456 Function and DOSAGE AND ADMINISTRATION).

457

458 **ADVERSE REACTIONS**

459 Several serious adverse events reported with lamivudine (lactic acidosis and severe
460 hepatomegaly with steatosis, posttreatment exacerbations of hepatitis B, pancreatitis, and

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

461 emergence of viral mutants associated with reduced drug susceptibility and diminished treatment
462 response) are also described in WARNINGS and PRECAUTIONS.

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

467

468 **Table 5. Selected Clinical Adverse Events (≥5% Frequency) in 3 Placebo-Controlled**
469 **Clinical Trials in Adults During Treatment* (Studies 1-3)**

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

470 *Includes patients treated for 52 to 68 weeks.

471

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

472 **Table 6. Frequencies of Specified Laboratory Abnormalities in 3 Placebo-Controlled Trials**
473 **in Adults During Treatment* (Studies 1-3)**

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

474 * Includes patients treated for 52 to 68 weeks.

475 [†] See Table 7 for posttreatment ALT values.

476 [‡] Includes observations during and after treatment in the 2 placebo-controlled trials that
477 collected this information.

478 ULN = Upper limit of normal.

479

480 In patients followed for up to 16 weeks after discontinuation of treatment, posttreatment ALT
481 elevations were observed more frequently in patients who had received EPIVIR-HBV than in
482 patients who had received placebo. A comparison of ALT elevations between weeks 52 and 68 in
483 patients who discontinued EPIVIR-HBV at week 52 and patients in the same studies who
484 received placebo throughout the treatment course is shown in Table 7.

485

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

486 **Table 7. Posttreatment ALT Elevations in 2 Placebo-Controlled Studies in Adults With**
487 **No-Active-Treatment Follow-up (Studies 1 and 3)**

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

488 *Each patient may be represented in one or more category.

489 [†]Comparable to a Grade 3 toxicity in accordance with modified WHO criteria.

490 ULN = Upper limit of normal.

491

492 **Lamivudine in Patients with HIV:** In HIV-infected patients, safety information reflects a
493 higher dose of lamivudine (150 mg twice daily) than the dose used to treat chronic hepatitis B in
494 HIV-negative patients. In clinical trials using lamivudine as part of a combination regimen for
495 treatment of HIV infection, several clinical adverse events occurred more often in
496 lamivudine-containing treatment arms than in comparator arms. These included nasal signs and
497 symptoms (20% vs. 11%), dizziness (10% vs. 4%), and depressive disorders (9% vs. 4%).
498 Pancreatitis was observed in 9 of the 2,613 adult patients (<0.5%) who received EPIVIR in
499 controlled clinical trials. Laboratory abnormalities reported more often in lamivudine-containing
500 arms included neutropenia and elevations of liver function tests (also more frequent in
501 lamivudine-containing arms for a retrospective analysis of HIV/HBV dually infected patients in
502 one study), and amylase elevations. Please see the complete prescribing information for EPIVIR
503 Tablets and Oral Solution for more information.

504 **Pediatric Patients with Hepatitis B:** Most commonly observed adverse events in the
505 pediatric trials were similar to those in adult trials; in addition, respiratory symptoms (cough,
506 bronchitis, and viral respiratory infections) were reported in both lamivudine and placebo

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

507 recipients. Posttreatment transaminase elevations were observed in some patients followed after
508 cessation of lamivudine.

509 **Pediatric Patients with HIV Infection:** In early open-label studies of lamivudine in children
510 with HIV, peripheral neuropathy and neutropenia were reported, and pancreatitis was observed in
511 14% to 15% of patients.

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

518 ***Digestive:*** Stomatitis.

519 ***Endocrine and Metabolic:*** Hyperglycemia.

520 ***General:*** Weakness.

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

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

525 ***Hypersensitivity:*** Anaphylaxis, urticaria.

526 ***Musculoskeletal:*** Rhabdomyolysis.

527 ***Nervous:*** Paresthesia, peripheral neuropathy.

528 ***Respiratory:*** Abnormal breath sounds/wheezing.

529 ***Skin:*** Alopecia, pruritus, rash.

530

531 **OVERDOSAGE**

532 There is no known antidote for EPIVIR-HBV. One case of an adult ingesting 6 g of EPIVIR
533 was reported; there were no clinical signs or symptoms noted and hematologic tests remained
534 normal. It is not known whether lamivudine can be removed by peritoneal dialysis or
535 hemodialysis. If overdose occurs, the patient should be monitored, and standard supportive
536 treatment applied as required.

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

537

538 **DOSAGE AND ADMINISTRATION**

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

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

548 **Pediatric Patients:** The recommended oral dose of EPIVIR-HBV for pediatric patients 2 to
549 17 years of age with chronic hepatitis B is 3 mg/kg once daily up to a maximum daily dose of
550 100 mg. Safety and effectiveness of treatment beyond 1 year have not been established and the
551 optimum duration of treatment is not known (see PRECAUTIONS).

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

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

557

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

558 **Table 8. Adjustment of Adult Dosage of EPIVIR-HBV in Accordance With**
559 **Creatinine Clearance**

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

560

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

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

566

567 **HOW SUPPLIED**

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

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

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

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

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

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

579

580 **REFERENCES**

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

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

584
585



586
587 GlaxoSmithKline
588 Research Triangle Park, NC 27709

589
590 Manufactured under agreement from
591 **Shire Pharmaceuticals Group plc**
592 Basingstoke, UK

593
594 ©2003, GlaxoSmithKline
595 All rights reserved.

596
597 August 2003 RL-2034

598
599

600 PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

601 -----

602
603

PATIENT INFORMATION

604
605 **EPIVIR -HBV[®] (lamivudine) Tablets**
606 **EPIVIR-HBV[®] (lamivudine) Oral Solution**

607
608 Please read this information before you start taking EPIVIR-HBV (pronounced EP-i-veer h-b-v).
609 Re-read it each time you get your prescription, in case some information has changed. **This**

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

610 **information does not take the place of careful discussions with your doctor when you start**
611 **this medication and at checkups. Stay under a doctor’s care when you take EPIVIR-HBV**
612 **and do not change or stop treatment without first talking with your doctor.**

613

614 **What is EPIVIR-HBV?**

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

618

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

621 EPIVIR-HBV contains a lower dose of lamivudine than the dose in EPIVIR[®], COMBIVIR[®], and
622 TRIZIVIR[®].

623

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

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

632

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

634 People who have both chronic hepatitis B and HIV should not take EPIVIR-HBV. EPIVIR-HBV
635 Tablets and EPIVIR-HBV Oral Solution contain a lower dose of the same drug (lamivudine) as
636 EPIVIR Tablets, EPIVIR Oral Solution, COMBIVIR Tablets, and TRIZIVIR Tablets. If you have
637 both hepatitis B and HIV, make sure that your doctor or healthcare provider is aware that you
638 have both infections. If you are prescribed lamivudine as part of your combination treatment for
639 HIV, you should use only the products and doses that are intended for treatment of HIV infection,

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

640 because the lower dose of lamivudine in EPIVIR-HBV could cause the HIV virus to be less
641 responsive to treatment. If you are planning to change your HIV treatment to a regimen that does
642 not include EPIVIR, COMBIVIR, or TRIZIVIR, you should first discuss this change with your
643 doctor or healthcare provider.

644

645 **Does EPIVIR-HBV cure hepatitis B infection?**

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

650

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

655

656 **What happens if I stop taking EPIVIR-HBV?**

657 After stopping treatment with EPIVIR-HBV, some patients have had symptoms or blood tests
658 showing that their hepatitis has gotten worse. Therefore, your doctor should check your health,
659 which may include blood tests, for at least several months after stopping treatment with
660 EPIVIR-HBV. Tell your doctor right away about any new or unusual symptoms that you notice
661 after stopping treatment.

662

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

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

668

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

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

671

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

673

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

675

676 **Can pregnant women and nursing mothers take EPIVIR-HBV?**

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

679

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

682

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

686

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

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

695

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

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

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

701

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

708

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

710

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

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

716

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

721

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

726

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

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

730

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

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

735

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

738 Talk to your doctor or healthcare provider if:

- 739 • You have HIV infection.
- 740 • You are pregnant or if you become pregnant while taking EPIVIR-HBV.
- 741 • You are breastfeeding.
- 742 • You have diabetes. Each 20-mL dose (100 mg) of EPIVIR-HBV Oral Solution contains
743 4 grams of sucrose.

744

745 Also talk to your doctor or healthcare provider about:

- 746 • Problems with your blood counts.
- 747 • Problems with your muscles.
- 748 • Problems with your kidneys.
- 749 • Problems with your pancreas.
- 750 • Any side effects or unusual symptoms during treatment.

751

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

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

755

756 **Other Information**

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

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

759

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

762

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

765



766

767 GlaxoSmithKline

768 Research Triangle Park, NC 27709

769

770 Manufactured under agreement from

771 **Shire Pharmaceuticals Group plc**

772 Basingstoke, UK

773

774 ©2003, GlaxoSmithKline

775 All rights reserved.

776

777 August 2003

RL-2034

778