

PRESCRIBING INFORMATION

EPIVIR-HBV[®]
(lamivudine)
Tablets

EPIVIR-HBV[®]
(lamivudine)
Oral Solution

WARNING

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

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

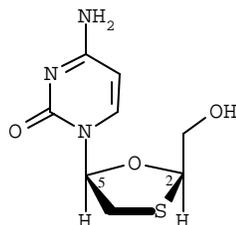
SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO HAVE DISCONTINUED ANTI-HEPATITIS B THERAPY (INCLUDING EPIVIR-HBV). HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE ANTI-HEPATITIS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

DESCRIPTION

EPIVIR-HBV is a brand name for lamivudine, a synthetic nucleoside analogue with activity against hepatitis B virus (HBV) and HIV. Lamivudine was initially developed for the treatment of HIV infection as EPIVIR. Please see the complete prescribing information for EPIVIR Tablets and Oral Solution for additional information. The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)-enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)-2',3'-

39 dideoxy, 3'-thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of
40 229.3. It has the following structural formula:

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42

43

44 Lamivudine is a white to off-white crystalline solid with a solubility of approximately
45 70 mg/mL in water at 20°C.

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

50 **EPIVIR-HBV Oral Solution** is for oral administration. One milliliter (1 mL) of
51 EPIVIR-HBV Oral Solution contains 5 mg of lamivudine (5 mg/mL) in an aqueous solution and
52 the inactive ingredients artificial strawberry and banana flavors, citric acid (anhydrous),
53 methylparaben, propylene glycol, propylparaben, sodium citrate (dihydrate), and sucrose
54 (200 mg).

55 MICROBIOLOGY

56 **Mechanism of Action:** Lamivudine is a synthetic nucleoside analogue. Lamivudine is
57 phosphorylated intracellularly to lamivudine triphosphate, L-TP. Incorporation of the
58 monophosphate form into viral DNA by HBV polymerase results in DNA chain termination.
59 L-TP also inhibits the RNA- and DNA-dependent DNA polymerase activities of HIV-1 reverse
60 transcriptase (RT). L-TP is a weak inhibitor of mammalian alpha-, beta-, and gamma-DNA
61 polymerases.

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

68 **Drug Resistance: HBV:** Genotypic analysis of viral isolates obtained from patients who show
69 renewed evidence of replication of HBV while receiving lamivudine suggests that a reduction in
70 sensitivity of HBV to lamivudine is associated with mutations resulting in a methionine to valine
71 or isoleucine substitution in the YMDD motif of the catalytic domain of HBV polymerase

72 (position 552) and a leucine to methionine substitution at position 528. It is not known whether
73 other HBV mutations may be associated with reduced lamivudine susceptibility in vitro.

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

82 In a controlled trial in pediatric patients, YMDD-mutant HBV were detected in 31 of 166
83 (19%) patients receiving lamivudine for 52 weeks. For a subgroup who remained on lamivudine
84 therapy in a follow-up study, YMDD mutations increased from 24% at 12 months to 45% (53 of
85 118) at 18 months of lamivudine treatment.

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

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

93 **CLINICAL PHARMACOLOGY**

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

97 The pharmacokinetic properties of lamivudine have also been studied in asymptomatic,
98 HIV-infected adult patients after administration of single intravenous (IV) doses ranging from
99 0.25 to 8 mg/kg, as well as single and multiple (twice-daily regimen) oral doses ranging from
100 0.25 to 10 mg/kg.

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

111 between the solution and the tablet. Therefore, the solution and the tablet may be used
112 interchangeably.

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

115 The 100-mg tablet was administered orally to 24 healthy subjects on 2 occasions, once in the
116 fasted state and once with food (standard meal: 967 kcal; 67 grams fat, 33 grams protein,
117 58 grams carbohydrate). There was no significant difference in systemic exposure (AUC_{∞}) in
118 the fed and fasted states; therefore, EPIVIR-HBV Tablets and Oral Solution may be administered
119 with or without food.

120 Lamivudine was rapidly absorbed after oral administration in HIV-infected patients. Absolute
121 bioavailability in 12 adult patients was $86\% \pm 16\%$ (mean \pm SD) for the 150-mg tablet and
122 $87\% \pm 13\%$ for the 10-mg/mL oral solution.

123 **Distribution:** The apparent volume of distribution after IV administration of lamivudine to
124 20 asymptomatic HIV-infected patients was 1.3 ± 0.4 L/kg, suggesting that lamivudine
125 distributes into extravascular spaces. Volume of distribution was independent of dose and did not
126 correlate with body weight.

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

131 **Metabolism:** Metabolism of lamivudine is a minor route of elimination. In man, the only
132 known metabolite of lamivudine is the trans-sulfoxide metabolite. In 9 healthy subjects receiving
133 300 mg of lamivudine as single oral doses, a total of 4.2% (range 1.5% to 7.5%) of the dose was
134 excreted as the trans-sulfoxide metabolite in the urine, the majority of which was excreted in the
135 first 12 hours.

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

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

142 In most single-dose studies in HIV- or HBV-infected patients or healthy subjects with serum
143 sampling for 24 hours after dosing, the observed mean elimination half-life ($t_{1/2}$) ranged from 5 to
144 7 hours. In HIV-infected patients, total clearance was 398.5 ± 69.1 mL/min (mean \pm SD). Oral
145 clearance and elimination half-life were independent of dose and body weight over an oral
146 dosing range from 0.25 to 10 mg/kg.

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

150

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

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

153 Exposure (AUC_∞), C_{max}, and half-life increased with diminishing renal function (as expressed
 154 by creatinine clearance). Apparent total oral clearance (Cl/F) of lamivudine decreased as
 155 creatinine clearance decreased. T_{max} was not significantly affected by renal function. Based on
 156 these observations, it is recommended that the dosage of lamivudine be modified in patients with
 157 renal impairment (see DOSAGE AND ADMINISTRATION).
 158

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

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

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

168 **Adults With Impaired Hepatic Function:** The pharmacokinetic properties of lamivudine
 169 have been determined in adults with impaired hepatic function (Table 2). Patients were stratified
 170 by severity of hepatic functional impairment.
 171

Deleted: is
 Deleted: peritoneal dialysis or

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

Parameter	Impairment*		
	Normal (n = 8)	Moderate (n = 8)	Severe (n = 8)
C _{max} (mcg/mL)	0.92 ± 0.31	1.06 ± 0.58	1.08 ± 0.27
AUC _∞ (mcg•hr/mL)	3.96 ± 0.58	3.97 ± 1.36	4.30 ± 0.63
T _{max} (hr)	1.3 ± 0.8	1.4 ± 0.8	1.4 ± 1.2
Cl/F (mL/min)	424.7 ± 61.9	456.9 ± 129.8	395.2 ± 51.8
Cl _r (mL/min)	279.2 ± 79.2	323.5 ± 100.9	216.1 ± 58.0

174 *Hepatic impairment assessed by aminopyrine breath test.

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

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

188 **Pediatric Patients** Lamivudine pharmacokinetics were evaluated in a 28-day dose-ranging
 189 study in 53 pediatric patients with chronic hepatitis B. Patients aged 2 to 12 years were
 190 randomized to receive lamivudine 0.35 mg/kg twice daily, 3 mg/kg once daily, 1.5 mg/kg twice
 191 daily, or 4 mg/kg twice daily. Patients aged 13 to 17 years received lamivudine 100 mg once
 192 daily. Lamivudine was rapidly absorbed (T_{max} 0.5 to 1 hour). In general, both C_{max} and exposure
 193 (AUC) showed dose proportionality in the dosing range studied. Weight-corrected oral clearance
 194 was highest at age 2 and declined from 2 to 12 years, where values were then similar to those
 195 seen in adults. A dose of 3 mg/kg given once daily produced a steady-state lamivudine AUC
 196 (mean 5,953 ng•hr/mL ± 1,562 SD) similar to that associated with a dose of 100 mg/day in
 197 adults.

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

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

200 **Drug Interactions:** Multiple doses of lamivudine and a single dose of interferon were
 201 coadministered to 19 healthy male subjects in a pharmacokinetics study. Results indicated a
 202 small (10%) reduction in lamivudine AUC, but no change in interferon pharmacokinetic

203 parameters when the 2 drugs were given in combination. All other pharmacokinetic parameters
204 (C_{max} , T_{max} , and $t_{1/2}$) were unchanged. There was no significant pharmacokinetic interaction
205 between lamivudine and interferon alfa in this study.

206 Lamivudine and zidovudine were coadministered to 12 asymptomatic HIV-positive adult
207 patients in a single-center, open-label, randomized, crossover study. No significant differences
208 were observed in AUC_{∞} or total clearance for lamivudine or zidovudine when the 2 drugs were
209 administered together. Coadministration of lamivudine with zidovudine resulted in an increase of
210 $39\% \pm 62\%$ (mean \pm SD) in C_{max} of zidovudine.

211 Lamivudine and trimethoprim/sulfamethoxazole (TMP/SMX) were coadministered to 14
212 HIV-positive patients in a single-center, open-label, randomized, crossover study. Each patient
213 received treatment with a single 300-mg dose of lamivudine and TMP 160 mg/SMX 800 mg
214 once a day for 5 days with concomitant administration of lamivudine 300 mg with the fifth dose
215 in a crossover design. Coadministration of TMP/SMX with lamivudine resulted in an increase of
216 $44\% \pm 23\%$ (mean \pm SD) in lamivudine AUC_{∞} , a decrease of $29\% \pm 13\%$ in lamivudine oral
217 clearance, and a decrease of $30\% \pm 36\%$ in lamivudine renal clearance. The pharmacokinetic
218 properties of TMP and SMX were not altered by coadministration with lamivudine (see
219 PRECAUTIONS: Drug Interactions).

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

222 INDICATIONS AND USAGE

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

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

- 237 • Study 1 was a randomized, double-blind study of EPIVIR-HBV 100 mg once daily versus
238 placebo for 52 weeks followed by a 16-week no-treatment period in treatment-naive US
239 patients.

- 240 • Study 2 was a randomized, double-blind, 3-arm study that compared EPIVIR-HBV 25 mg
 241 once daily versus EPIVIR-HBV 100 mg once daily versus placebo for 52 weeks in Asian
 242 patients.
- 243 • Study 3 was a randomized, partially-blind, 3-arm study conducted primarily in North
 244 America and Europe in patients who had ongoing evidence of active chronic hepatitis B
 245 despite previous treatment with interferon alfa. The study compared EPIVIR-HBV 100 mg
 246 once daily for 52 weeks, followed by either EPIVIR-HBV 100 mg or matching placebo
 247 once daily for 16 weeks (Arm 1), versus placebo once daily for 68 weeks (Arm 2). (A third
 248 arm using a combination of interferon and lamivudine is not presented here because there
 249 was not sufficient information to evaluate this regimen.)

250 Principal endpoint comparisons for the histologic and serologic outcomes in lamivudine
 251 (100 mg daily) and placebo recipients in placebo-controlled studies are shown in the following
 252 tables.

254 **Table 3. Histologic Response at Week 52 Among Adult Patients Receiving EPIVIR-HBV**
 255 **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%

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

260 **Table 4. HBeAg Seroconversion* at Week 52 Among Adult Patients Receiving**
 261 **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%

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

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

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

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

286 **CONTRAINDICATIONS**

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

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
295 factors. Most of these reports have described patients receiving nucleoside analogues for
296 treatment of HIV infection, but there have been reports of lactic acidosis in patients receiving
297 lamivudine for hepatitis B. Particular caution should be exercised when administering EPIVIR or
298 EPIVIR-HBV to any patient with known risk factors for liver disease; however, cases have also
299 been reported in patients with no known risk factors. Treatment with EPIVIR or EPIVIR-HBV
300 should be suspended in any patient who develops clinical or laboratory findings suggestive of
301 lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis
302 even in 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
305 contain a lower dose of the same active ingredient (lamivudine) as EPIVIR Tablets and Oral
306 Solution, COMBIVIR[®] (lamivudine/zidovudine) Tablets, and TRIZIVIR[®] (abacavir, lamivudine,

307 and zidovudine) Tablets used to treat HIV infection. The formulation and dosage of lamivudine
308 in EPIVIR-HBV are not appropriate for patients dually infected with HBV and HIV. If a
309 decision is made to administer lamivudine to such patients, the higher dosage indicated for HIV
310 therapy should be used as part of an appropriate combination regimen, and the prescribing
311 information for EPIVIR , COMBIVIR, or TRIZIVIR as well as for EPIVIR-HBV should be
312 consulted. HIV counseling and testing should be offered to all patients before beginning
313 EPIVIR-HBV and periodically during treatment because of the risk of rapid emergence of
314 resistant HIV and limitation of treatment options if EPIVIR-HBV is prescribed to treat chronic
315 hepatitis B in a patient who has unrecognized or untreated HIV infection or acquires HIV
316 infection during 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 **PRECAUTIONS**

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

332 **Emergence of Resistance-Associated HBV Mutations:** In controlled clinical trials,
333 YMDD-mutant HBV were detected in patients with on-lamivudine re-appearance of HBV DNA
334 after an initial decline below the solution-hybridization assay limit (see MICROBIOLOGY:
335 Drug Resistance). These mutations can be detected by a research assay and have been associated
336 with reduced susceptibility to lamivudine in vitro. Lamivudine-treated patients (adult and
337 pediatric) with YMDD-mutant HBV at 52 weeks showed diminished treatment responses in
338 comparison to lamivudine-treated patients without evidence of YMDD mutations, including
339 lower rates of HBeAg seroconversion and HBeAg loss (no greater than placebo recipients), more
340 frequent return of positive HBV DNA by solution-hybridization or branched-chain DNA assay,
341 and more frequent ALT elevations. In the controlled trials, when patients developed
342 YMDD-mutant HBV, they had a rise in HBV DNA and ALT from their own previous
343 on-treatment levels. Progression of hepatitis B, including death, has been reported in some
344 patients with YMDD-mutant HBV, including patients from the liver transplant setting and from
345 other clinical trials. The long-term clinical significance of YMDD-mutant HBV is not known.

346 Increased clinical and laboratory monitoring may aid in treatment decisions if emergence of viral
347 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.

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 when treatment was discontinued. Patients should be advised
378 to discuss any changes in regimen with their physician.

379 Patients should be informed that emergence of resistant hepatitis B virus and worsening of
380 disease can occur during treatment, and they should promptly report any new symptoms to their
381 physician.

382 Patients should be counseled on the importance of testing for HIV to avoid inappropriate
383 therapy and development of resistant HIV, and HIV counseling and testing should be offered
384 before starting EPIVIR-HBV and periodically during therapy. Patients should be advised that
385 EPIVIR-HBV Tablets and EPIVIR-HBV Oral Solution contain a lower dose of the same active

386 ingredient (lamivudine) as EPIVIR Tablets, EPIVIR Oral Solution, COMBIVIR Tablets, and
387 TRIZIVIR Tablets. EPIVIR-HBV should not be taken concurrently with EPIVIR, COMBIVIR,
388 or TRIZIVIR (see WARNINGS). Patients infected with both HBV and HIV who are planning to
389 change their HIV treatment regimen to a regimen that does not include EPIVIR, COMBIVIR, or
390 TRIZIVIR should discuss continued therapy for hepatitis B with their physician.

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

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

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

400 TMP 160 mg/SMX 800 mg once daily has been shown to increase lamivudine exposure
401 (AUC) by 44% (see CLINICAL PHARMACOLOGY). No change in dose of either drug is
402 recommended. There is no information regarding the effect on lamivudine pharmacokinetics of
403 higher doses of TMP/SMX such as those used to treat *Pneumocystis carinii* pneumonia. No data
404 are available regarding interactions with other drugs that have renal clearance mechanisms
405 similar to that of lamivudine.

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

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

420 **Pregnancy:** Pregnancy Category C. Reproduction studies have been performed in rats and
421 rabbits at orally administered doses up to 4,000 mg/kg/day and 1,000 mg/kg/day, respectively,
422 producing plasma levels up to approximately 60 times that for the adult HBV dose. No evidence
423 of teratogenicity due to lamivudine was observed. Evidence of early embryoletality was seen in
424 the rabbit at exposure levels similar to those observed in humans, but there was no indication of
425 this effect in the rat at exposures up to 60 times that in humans. Studies in pregnant rats and

426 rabbits showed that lamivudine is transferred to the fetus through the placenta. There are no
427 adequate and well-controlled studies in pregnant women. Because animal reproductive toxicity
428 studies are not always predictive of human response, lamivudine should be used during
429 pregnancy only if the potential benefits outweigh the risks.

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

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

435 **Nursing Mothers:** A study in lactating rats administered 45 mg/kg of lamivudine showed that
436 lamivudine concentrations in milk were slightly greater than those in plasma. Lamivudine is also
437 excreted in human milk. Samples of breast milk obtained from 20 mothers receiving lamivudine
438 monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice daily and
439 300 mg zidovudine twice daily) had measurable concentrations of lamivudine.

440 Because of the potential for serious adverse reactions in nursing infants, **mothers should be**
441 **instructed not to breastfeed if they are 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
453 therapy. In particular, because lamivudine is substantially excreted by the kidney and elderly
454 patients are more likely to have decreased renal function, renal function should be monitored and
455 dosage adjustments should be made accordingly (see PRECAUTIONS: Patients with Impaired
456 Renal Function and DOSAGE AND ADMINISTRATION).

457 **ADVERSE REACTIONS**

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

462 **Clinical Trials In Chronic Hepatitis B: Adults:** Selected clinical adverse events observed
463 with a $\geq 5\%$ frequency during therapy with EPIVIR-HBV compared with placebo are listed in

464 Table 5. Frequencies of specified laboratory abnormalities during therapy with EPIVIR-HBV
 465 compared with placebo are listed in Table 6.

466

467 **Table 5. Selected Clinical Adverse Events ([≥]5% Frequency) in 3 Placebo-Controlled**

468 **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%

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469 *Includes patients treated for 52 to 68 weeks.

470

471 **Table 6. Frequencies of Specified Laboratory Abnormalities in 3 Placebo-Controlled Trials**
 472 **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%)

473 * Includes patients treated for 52 to 68 weeks.

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

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

477 ULN = Upper limit of normal.

478

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

484

485 **Table 7. Posttreatment ALT Elevations in 2 Placebo-Controlled Studies in Adults With**
486 **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%)

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

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

489 ULN = Upper limit of normal.

490

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

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

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

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

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

517 **Digestive:** Stomatitis.

518 **Endocrine and Metabolic:** Hyperglycemia.

519 **General:** Weakness.

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

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

524 **Hypersensitivity:** Anaphylaxis, urticaria.

525 **Musculoskeletal:** Rhabdomyolysis.

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

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

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

529 OVERDOSAGE

530 There is no known antidote for EPIVIR-HBV. One case of an adult ingesting 6 g of EPIVIR
531 was reported; there were no clinical signs or symptoms noted and hematologic tests remained
532 normal. ~~Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis,
533 continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if
534 continuous hemodialysis would provide clinical benefit in a lamivudine overdose event. If
535 overdose occurs, the patient should be monitored, and standard supportive treatment applied as
536 required.~~

Deleted: It is not known whether lamivudine can be removed by peritoneal dialysis or hemodialysis.

537 DOSAGE AND ADMINISTRATION

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

542 **The formulation and dosage of lamivudine in EPIVIR-HBV are not appropriate for
543 patients dually infected with HBV and HIV. If lamivudine is administered to such patients,
544 the higher dosage indicated for HIV therapy should be used as part of an appropriate**

545 combination regimen, and the prescribing information for EPIVIR as well as
546 EPIVIR-HBV should be consulted.

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

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

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

557 **Table 8. Adjustment of Adult Dosage of EPIVIR-HBV in Accordance With**
558 **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

559
560 No additional dosing of EPIVIR-HBV is required after routine (4-hour) hemodialysis or
561 peritoneal dialysis.
562 Although there are insufficient data to recommend a specific dose adjustment of
563 EPIVIR-HBV in pediatric patients with renal impairment, a dose reduction should be considered.

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

565 **HOW SUPPLIED**

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

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

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

577 **REFERENCES**

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

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582



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584 GlaxoSmithKline
585 Research Triangle Park, NC 27709

586
587 Manufactured under agreement from
588 **Shire Pharmaceuticals Group plc**
589 Basingstoke, UK

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594 May 2004 RL-2089

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PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

600 **PATIENT INFORMATION**

601
602 **EPIVIR -HBV[®] (lamivudine) Tablets**
603 **EPIVIR-HBV[®] (lamivudine) Oral Solution**

604
605 Please read this information before you start taking EPIVIR-HBV (pronounced EP-i-veer h-b-v).
606 Re-read it each time you get your prescription, in case some information has changed. **This**
607 **information does not take the place of careful discussions with your doctor when you start**
608 **this medication and at checkups. Stay under a doctor's care when you take EPIVIR-HBV**
609 **and do not change or stop treatment without first talking with your doctor.**

610
611 **What is EPIVIR-HBV?**
612 EPIVIR-HBV is the brand name of a product that contains lamivudine, a drug used to treat
613 chronic hepatitis B in patients with actively growing virus and liver inflammation. Hepatitis B
614 can cause damage to cells in the liver. Eventually, this can scar the liver.

615
616 The lamivudine in EPIVIR-HBV can reduce the ability of the hepatitis B virus to multiply and
617 infect new liver cells. It may help to lower the amount of hepatitis B virus in your body.
618 EPIVIR-HBV contains a lower dose of lamivudine than the dose in EPIVIR[®], COMBIVIR[®], and
619 TRIZIVIR[®].

620

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

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

629

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

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

641

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

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

647

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

652

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

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

659

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

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

665

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

668

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

670

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

672

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

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

676

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

679

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

683

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

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

692

693 If you miss your regular time for taking your dose, but then remember it during that same day,
694 take your missed dose immediately. Then, take your next dose at the regularly scheduled time
695 the following day. Do **not** take 2 doses of EPIVIR-HBV at once to make up for missing a dose.
696 If you are not sure what to do if you miss taking your medication, check with your doctor or
697 healthcare provider for further instructions.

698
699 EPIVIR-HBV can usually be taken with many other medications; however, be sure to tell your
700 doctor or healthcare provider about all medications (including over-the-counter and prescription
701 drugs) that you are taking. EPIVIR-HBV Tablets and EPIVIR-HBV Oral Solution contain a
702 lower dose of the same drug (lamivudine) as EPIVIR Tablets, EPIVIR Oral Solution,
703 COMBIVIR Tablets, and TRIZIVIR Tablets; therefore, EPIVIR-HBV should not be taken
704 together with EPIVIR, COMBIVIR, or TRIZIVIR.

705
706 You should talk to your doctor about any changes in your treatment.

707
708 **What are the possible side effects of EPIVIR-HBV?**

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

713
714 Hepatitis B virus sometimes becomes resistant to EPIVIR-HBV during treatment, and some
715 people have had tests showing that their hepatitis was getting worse around the time the virus
716 became resistant. Some people also have worsening of hepatitis after stopping EPIVIR-HBV.
717 You should discuss any change in treatment with your doctor.

718
719 In studies, the most common side effects seen during treatment with EPIVIR-HBV were ear,
720 nose, and throat infections; malaise and fatigue (feeling tired and run down); headache;
721 abdominal discomfort and pain; nausea and vomiting; diarrhea; muscle pain; sore throat; joint
722 pain; fever or chills; and skin rash.

723
724 This list of possible side effects is not complete. Your doctor or pharmacist can discuss with you
725 a more complete list of possible side effects with EPIVIR-HBV. Talk to your doctor right away
726 about any side effects or other unusual symptoms that occur when taking EPIVIR-HBV.

727

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

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

732

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

735 Talk to your doctor or healthcare provider if:

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

741

742 Also talk to your doctor or healthcare provider about:

- 743 • Problems with your blood counts.
- 744 • Problems with your muscles.
- 745 • Problems with your kidneys.
- 746 • Problems with your pancreas.
- 747 • Any side effects or unusual symptoms during treatment.

748

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

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

752

753 **Other Information**

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

756

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

759

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

762



763 **GlaxoSmithKline**

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764 GlaxoSmithKline

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765 Research Triangle Park, NC 27709

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767 Manufactured under agreement from

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768 **Shire Pharmaceuticals Group plc**

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769 Basingstoke, UK

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774 May 2004

RL-2089