

1 PRESCRIBING INFORMATION

2 **EPIVIR[®] Tablets**
3 **(lamivudine tablets)**

4
5 **EPIVIR[®] Oral Solution**
6 **(lamivudine oral solution)**
7

8 **WARNING**

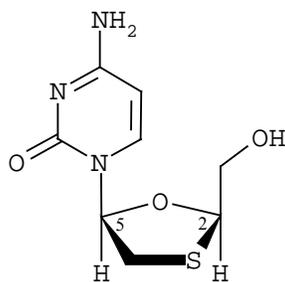
9 **LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS,**
10 **INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF**
11 **NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING**
12 **LAMIVUDINE AND OTHER ANTIRETROVIRALS (SEE WARNINGS).**

13 **EPIVIR TABLETS AND ORAL SOLUTION (USED TO TREAT HIV INFECTION)**
14 **CONTAIN A HIGHER DOSE OF THE ACTIVE INGREDIENT (LAMIVUDINE) THAN**
15 **EPIVIR-HBV[®] TABLETS AND ORAL SOLUTION (USED TO TREAT CHRONIC**
16 **HEPATITIS B). PATIENTS WITH HIV INFECTION SHOULD RECEIVE ONLY**
17 **DOSING FORMS APPROPRIATE FOR TREATMENT OF HIV (SEE WARNINGS AND**
18 **PRECAUTIONS).**

19 **SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED**
20 **IN PATIENTS WHO ARE CO-INFECTED WITH HEPATITIS B VIRUS (HBV) AND**
21 **HIV AND HAVE DISCONTINUED EPIVIR. HEPATIC FUNCTION SHOULD BE**
22 **MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-**
23 **UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE**
24 **EPIVIR AND ARE CO-INFECTED WITH HIV AND HBV. IF APPROPRIATE,**
25 **INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE**
26 **WARNINGS).**

27 **DESCRIPTION**

28 EPIVIR (also known as 3TC) is a brand name for lamivudine, a synthetic nucleoside analogue
29 with activity against human immunodeficiency virus-1 (HIV-1) and hepatitis B virus (HBV).
30 The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-
31 (1H)-pyrimidin-2-one. Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine.
32 Lamivudine has also been referred to as (-)2',3'-dideoxy, 3'-thiacytidine. It has a molecular
33 formula of C₈H₁₁N₃O₃S and a molecular weight of 229.3. It has the following structural formula:
34



35
36

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

39 **EPIVIR Tablets** are for oral administration. Each 150-mg film-coated tablet contains 150 mg
40 of lamivudine and the inactive ingredients hypromellose, magnesium stearate, microcrystalline
41 cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide.

42 Each 300-mg film-coated tablet contains 300 mg of lamivudine and the inactive ingredients
43 black iron oxide, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene
44 glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide.

45 **EPIVIR Oral Solution** is for oral administration. One milliliter (1 mL) of EPIVIR Oral
46 Solution contains 10 mg of lamivudine (10 mg/mL) in an aqueous solution and the inactive
47 ingredients artificial strawberry and banana flavors, citric acid (anhydrous), methylparaben,
48 propylene glycol, propylparaben, sodium citrate (dihydrate), and sucrose (200 mg).

49 **MICROBIOLOGY**

50 **Mechanism of Action:** Lamivudine is a synthetic nucleoside analogue. Intracellularly,
51 lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate
52 (L-TP). The principal mode of action of L-TP is the inhibition of HIV-1 reverse transcriptase
53 (RT) via DNA chain termination after incorporation of the nucleoside analogue into viral DNA.
54 L-TP is a weak inhibitor of mammalian DNA polymerases α and β , and mitochondrial DNA
55 polymerase γ .

56 **Antiviral Activity In Vitro:** The in vitro activity of lamivudine against HIV-1 was assessed in
57 a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes)
58 using standard susceptibility assays. IC₅₀ values (50% inhibitory concentrations) were in the
59 range of 2 nM to 15 μ M. Lamivudine had anti-HIV-1 activity in all acute virus-cell infections
60 tested. In HIV-1–infected MT-4 cells, lamivudine in combination with zidovudine at various
61 ratios exhibited synergistic antiretroviral activity. The relationship between in vitro susceptibility
62 of HIV-1 to lamivudine and the inhibition of HIV-1 replication in humans has not been
63 established. Please see the EPIVIR-HBV package insert for information regarding the inhibitory
64 activity of lamivudine against HBV.

65 **Drug Resistance:** Lamivudine-resistant variants of HIV-1 have been selected in vitro.
66 Genotypic analysis showed that the resistance was due to a specific amino acid substitution in
67 the HIV-1 reverse transcriptase at codon 184 changing the methionine residue to either
68 isoleucine or valine.

69 HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from patients.
70 Susceptibility of clinical isolates to lamivudine and zidovudine was monitored in controlled
71 clinical trials. In patients receiving lamivudine monotherapy or combination therapy with
72 lamivudine plus zidovudine, HIV-1 isolates from most patients became phenotypically and
73 genotypically resistant to lamivudine within 12 weeks. In some patients harboring
74 zidovudine-resistant virus at baseline, phenotypic sensitivity to zidovudine was restored by
75 12 weeks of treatment with lamivudine and zidovudine. Combination therapy with lamivudine
76 plus zidovudine delayed the emergence of mutations conferring resistance to zidovudine.

77 Mutations in the HBV polymerase YMDD motif have been associated with reduced
78 susceptibility of HBV to lamivudine in vitro. In studies of non-HIV-infected patients with
79 chronic hepatitis B, HBV isolates with YMDD mutations were detected in some patients who
80 received lamivudine daily for 6 months or more, and were associated with evidence of
81 diminished treatment response; similar HBV mutants have been reported in HIV-infected
82 patients who received lamivudine-containing antiretroviral regimens in the presence of
83 concurrent infection with hepatitis B virus (see PRECAUTIONS and EPIVIR-HBV package
84 insert).

85 **Cross Resistance:** Lamivudine-resistant HIV-1 mutants were cross resistant to didanosine
86 (ddI) and zalcitabine (ddC). In some patients treated with zidovudine plus didanosine or
87 zalcitabine, isolates resistant to multiple reverse transcriptase inhibitors, including lamivudine,
88 have emerged.

89 ***Genotypic and Phenotypic Analysis of On-Therapy HIV-1 Isolates From***
90 ***Patients With Virologic Failure (see INDICATIONS AND USAGE: Description of***
91 ***Clinical Studies):*** The clinical relevance of genotypic and phenotypic changes associated with
92 lamivudine therapy has not been fully established.

93 ***Study EPV20001:*** Fifty-three of 554 (10%) patients enrolled in EPV20001 were
94 identified as virological failures (plasma HIV-1 RNA level ≥ 400 copies/mL) by Week 48.
95 Twenty-eight patients were randomized to the lamivudine once-daily treatment group and 25 to
96 the lamivudine twice-daily treatment group. The median baseline plasma HIV-1 RNA levels of
97 patients in the lamivudine once-daily group and lamivudine twice-daily group were
98 $4.9 \log_{10}$ copies/mL and $4.6 \log_{10}$ copies/mL, respectively.

99 Genotypic analysis of on-therapy isolates from 22 patients identified as virologic failures in
100 the lamivudine once-daily group showed that isolates from 0/22 patients contained
101 treatment-emergent mutations associated with zidovudine resistance (M41L, D67N, K70R,
102 L210W, T215Y/F, or K219Q/E), isolates from 10/22 patients contained treatment-emergent
103 mutations associated with efavirenz resistance (L100I, K101E, K103N, V108I, or Y181C), and
104 isolates from 8/22 patients contained a treatment-emergent lamivudine resistance-associated
105 mutation (M184I or M184V).

106 Genotypic analysis of on-therapy isolates from patients (n = 22) in the lamivudine twice-daily
107 treatment group showed that isolates from 1/22 patients contained treatment-emergent
108 zidovudine resistance mutations, isolates from 7/22 contained treatment-emergent efavirenz

109 resistance mutations, and isolates from 5/22 contained treatment-emergent lamivudine resistance
110 mutations.

111 Phenotypic analysis of baseline-matched on-therapy HIV-1 isolates from patients (n = 13)
112 receiving lamivudine once daily showed that isolates from 12/13 patients were susceptible to
113 zidovudine; isolates from 8/13 patients exhibited a 25- to 295-fold decrease in susceptibility to
114 efavirenz, and isolates from 7/13 patients showed an 85- to 299-fold decrease in susceptibility to
115 lamivudine.

116 Phenotypic analysis of baseline-matched on-therapy HIV-1 isolates from patients (n = 13)
117 receiving lamivudine twice daily showed that isolates from all 13 patients were susceptible to
118 zidovudine; isolates from 3/13 patients exhibited a 21- to 342-fold decrease in susceptibility to
119 efavirenz, and isolates from 4/13 patients exhibited a 29- to 159-fold decrease in susceptibility to
120 lamivudine.

121 **Study EPV40001:** Fifty patients received zidovudine 300 mg twice daily plus abacavir
122 300 mg twice daily plus lamivudine 300 mg once daily and 50 patients received zidovudine
123 300 mg plus abacavir 300 mg plus lamivudine 150 mg all twice daily. The median baseline
124 plasma HIV-1 RNA levels for patients in the 2 groups were 4.79 log₁₀ copies/mL and
125 4.83 log₁₀ copies/mL, respectively. Fourteen of 50 patients in the lamivudine once-daily
126 treatment group and 9 of 50 patients in the lamivudine twice-daily group were identified as
127 virologic failures.

128 Genotypic analysis of on-therapy HIV-1 isolates from patients (n = 9) in the lamivudine
129 once-daily treatment group showed that isolates from 6 patients had abacavir and/or lamivudine
130 resistance-associated mutation M184V alone. On-therapy isolates from patients (n = 6) receiving
131 lamivudine twice daily showed that isolates from 2 patients had M184V alone, and isolates from
132 2 patients harbored the M184V mutation in combination with zidovudine resistance-associated
133 mutations.

134 Phenotypic analysis of on-therapy isolates from patients (n = 6) receiving lamivudine once
135 daily showed that HIV-1 isolates from 4 patients exhibited a 32- to 53-fold decrease in
136 susceptibility to lamivudine. HIV-1 isolates from these 6 patients were susceptible to zidovudine.

137 Phenotypic analysis of on-therapy isolates from patients (n = 4) receiving lamivudine twice
138 daily showed that HIV-1 isolates from 1 patient exhibited a 45-fold decrease in susceptibility to
139 lamivudine and a 4.5-fold decrease in susceptibility to zidovudine.

140 **CLINICAL PHARMACOLOGY**

141 **Pharmacokinetics in Adults:** The steady-state pharmacokinetic properties of the EPIVIR
142 300-mg tablet once daily for 7 days compared to the EPIVIR 150-mg tablet twice daily for
143 7 days were assessed in a crossover study in 60 healthy volunteers. EPIVIR 300 mg once daily
144 resulted in lamivudine exposures that were similar to EPIVIR 150 mg twice daily with respect to
145 plasma AUC_{24,ss}; however, C_{max,ss} was 66% higher and the trough value was 53% lower
146 compared to the 150-mg twice-daily regimen. Intracellular lamivudine triphosphate exposures in
147 peripheral blood mononuclear cells were also similar with respect to AUC_{24,ss} and C_{max24,ss};

148 however, trough values were lower compared to the 150-mg twice-daily regimen. Inter-subject
149 variability was greater for intracellular lamivudine triphosphate concentrations versus
150 lamivudine plasma trough concentrations. The clinical significance of observed differences for
151 both plasma lamivudine concentrations and intracellular lamivudine triphosphate concentrations
152 is not known.

153 The pharmacokinetic properties of lamivudine have been studied in asymptomatic,
154 HIV-infected adult patients after administration of single intravenous (IV) doses ranging from
155 0.25 to 8 mg/kg, as well as single and multiple (twice-daily regimen) oral doses ranging from
156 0.25 to 10 mg/kg.

157 The pharmacokinetic properties of lamivudine have also been studied as single and multiple
158 oral doses ranging from 5 mg to 600 mg/day administered to HBV-infected patients.

159 **Absorption and Bioavailability:** Lamivudine was rapidly absorbed after oral
160 administration in HIV-infected patients. Absolute bioavailability in 12 adult patients was
161 $86\% \pm 16\%$ (mean \pm SD) for the 150-mg tablet and $87\% \pm 13\%$ for the oral solution. After oral
162 administration of 2 mg/kg twice a day to 9 adults with HIV, the peak serum lamivudine
163 concentration (C_{\max}) was 1.5 ± 0.5 mcg/mL (mean \pm SD). The area under the plasma
164 concentration versus time curve (AUC) and C_{\max} increased in proportion to oral dose over the
165 range from 0.25 to 10 mg/kg.

166 An investigational 25-mg dosage form of lamivudine was administered orally to
167 12 asymptomatic, HIV-infected patients on 2 occasions, once in the fasted state and once with
168 food (1,099 kcal; 75 grams fat, 34 grams protein, 72 grams carbohydrate). Absorption of
169 lamivudine was slower in the fed state (T_{\max} : 3.2 ± 1.3 hours) compared with the fasted state
170 (T_{\max} : 0.9 ± 0.3 hours); C_{\max} in the fed state was $40\% \pm 23\%$ (mean \pm SD) lower than in the
171 fasted state. There was no significant difference in systemic exposure (AUC_{∞}) in the fed and
172 fasted states; therefore, EPIVIR Tablets and Oral Solution may be administered with or without
173 food.

174 The accumulation ratio of lamivudine in HIV-positive asymptomatic adults with normal renal
175 function was 1.50 following 15 days of oral administration of 2 mg/kg twice daily.

176 **Distribution:** The apparent volume of distribution after IV administration of lamivudine to
177 20 patients was 1.3 ± 0.4 L/kg, suggesting that lamivudine distributes into extravascular spaces.
178 Volume of distribution was independent of dose and did not correlate with body weight.

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

182 **Metabolism:** Metabolism of lamivudine is a minor route of elimination. In man, the only
183 known metabolite of lamivudine is the trans-sulfoxide metabolite. Within 12 hours after a single
184 oral dose of lamivudine in 6 HIV-infected adults, $5.2\% \pm 1.4\%$ (mean \pm SD) of the dose was
185 excreted as the trans-sulfoxide metabolite in the urine. Serum concentrations of this metabolite
186 have not been determined.

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

192 In most single-dose studies in HIV-infected patients, HBV-infected patients, or healthy
 193 subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life
 194 ($t_{1/2}$) ranged from 5 to 7 hours. In HIV-infected patients, total clearance was
 195 398.5 ± 69.1 mL/min (mean \pm SD). Oral clearance and elimination half-life were independent of
 196 dose and body weight over an oral dosing range from 0.25 to 10 mg/kg.

197 **Special Populations: Adults with Impaired Renal Function:** The pharmacokinetic
 198 properties of lamivudine have been determined in a small group of HIV-infected adults with
 199 impaired renal function (Table 1).

200

201 **Table 1. Pharmacokinetic Parameters (Mean \pm SD) After a Single 300-mg Oral Dose of**
 202 **Lamivudine in 3 Groups of Adults With Varying Degrees of Renal Function**

Parameter	Creatinine Clearance Criterion (Number of Subjects)		
	>60 mL/min (n = 6)	10-30 mL/min (n = 4)	<10 mL/min (n = 6)
Creatinine clearance (mL/min)	111 ± 14	28 ± 8	6 ± 2
C_{max} (mcg/mL)	2.6 ± 0.5	3.6 ± 0.8	5.8 ± 1.2
AUC_{∞} (mcg•hr/mL)	11.0 ± 1.7	48.0 ± 19	157 ± 74
Cl/F (mL/min)	464 ± 76	114 ± 34	36 ± 11

203

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

209 Based on a study in otherwise healthy subjects with impaired renal function, hemodialysis
 210 increased lamivudine clearance from a mean of 64 to 88 mL/min; however, the length of time of
 211 hemodialysis (4 hours) was insufficient to significantly alter mean lamivudine exposure after a
 212 single-dose administration. Therefore, it is recommended, following correction of dose for
 213 creatinine clearance, that no additional dose modification be made after routine hemodialysis.

214 It is not known whether lamivudine can be removed by peritoneal dialysis or continuous
 215 (24-hour) hemodialysis.

216 The effects of renal impairment on lamivudine pharmacokinetics in pediatric patients are not
 217 known.

218 **Adults with Impaired Hepatic Function:** The pharmacokinetic properties of lamivudine
219 have been determined in adults with impaired hepatic function. Pharmacokinetic parameters
220 were not altered by diminishing hepatic function; therefore, no dose adjustment for lamivudine is
221 required for patients with impaired hepatic function. Safety and efficacy of lamivudine have not
222 been established in the presence of decompensated liver disease.

223 **Pediatric Patients:** For pharmacokinetic properties of lamivudine in pediatric patients, see
224 PRECAUTIONS: Pediatric Use.

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

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

227 **Drug Interactions:** No clinically significant alterations in lamivudine or zidovudine
228 pharmacokinetics were observed in 12 asymptomatic HIV-infected adult patients given a single
229 dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg q
230 12 hr).

231 Lamivudine and trimethoprim/sulfamethoxazole (TMP/SMX) were coadministered to 14
232 HIV-positive patients in a single-center, open-label, randomized, crossover study. Each patient
233 received treatment with a single 300-mg dose of lamivudine and TMP 160 mg/SMX 800 mg
234 once a day for 5 days with concomitant administration of lamivudine 300 mg with the fifth dose
235 in a crossover design. Coadministration of TMP/SMX with lamivudine resulted in an increase of
236 $44\% \pm 23\%$ (mean \pm SD) in lamivudine AUC_{∞} , a decrease of $29\% \pm 13\%$ in lamivudine oral
237 clearance, and a decrease of $30\% \pm 36\%$ in lamivudine renal clearance. The pharmacokinetic
238 properties of TMP and SMX were not altered by coadministration with lamivudine.

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

241 There was no significant pharmacokinetic interaction between lamivudine and interferon alfa
242 in a study of 19 healthy male subjects.

243 **INDICATIONS AND USAGE**

244 **EPIVIR in combination with other antiretroviral agents is indicated for the treatment of**
245 **HIV infection (see Description of Clinical Studies).**

246 **Description of Clinical Studies:** The use of EPIVIR is based on the results of clinical
247 studies in HIV-infected patients in combination regimens with other antiretroviral agents.
248 Information from trials with clinical endpoints or a combination of CD4+ cell counts and HIV-1
249 RNA measurements is included below as documentation of the contribution of lamivudine to a
250 combination regimen in controlled trials.

251 **Clinical Endpoint Study in Adults:** B3007 (CAESAR) was a multicenter, double-blind,
252 placebo-controlled study comparing continued current therapy (zidovudine alone [62% of
253 patients] or zidovudine with didanosine or zalcitabine [38% of patients]) to the addition of
254 EPIVIR or EPIVIR plus an investigational non-nucleoside reverse transcriptase inhibitor
255 (NNRTI), randomized 1:2:1. A total of 1,816 HIV-infected adults with 25 to 250
256 CD4+ cells/mm³ (median = 122 cells/mm³) at baseline were enrolled: median age was 36 years,

257 87% were male, 84% were nucleoside-experienced, and 16% were therapy-naive. The median
258 duration on study was 12 months. Results are summarized in Table 2.

259

260 **Table 2. Number of Patients (%) With At Least One HIV Disease Progression Event or**
261 **Death**

Endpoint	Current Therapy (n = 460)	EPIVIR plus Current Therapy (n = 896)	EPIVIR plus a NNRTI* plus Current Therapy (n = 460)
HIV progression or death	90 (19.6%)	86 (9.6%)	41 (8.9%)
Death	27 (5.9%)	23 (2.6%)	14 (3.0%)

262 *An investigational non-nucleoside reverse transcriptase inhibitor not approved in the United
263 States.

264

265 **Surrogate Endpoint Studies in Adults: Dual Nucleoside Analogue Studies:**

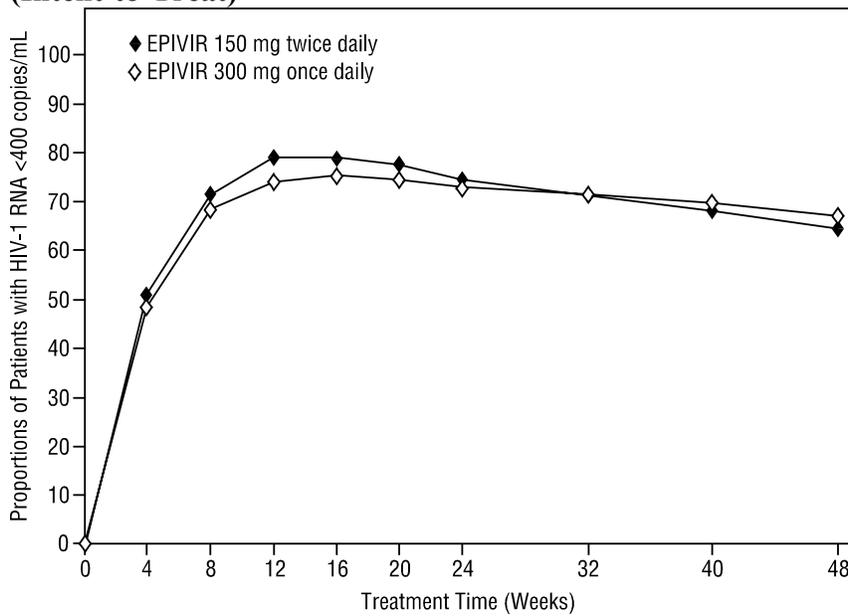
266 Principal clinical trials in the initial development of lamivudine compared
267 lamivudine/zidovudine combinations against zidovudine monotherapy or against zidovudine plus
268 zalcitabine. These studies demonstrated the antiviral effect of lamivudine in a 2-drug
269 combination. More recent uses of lamivudine in treatment of HIV infection incorporate it into
270 multiple-drug regimens containing at least 3 antiretroviral drugs for enhanced viral suppression.

271 **Dose Regimen Comparison Surrogate Endpoint Studies in Therapy-Naive**

272 **Adults:** EPV20001 was a multicenter, double-blind, controlled study in which patients were
273 randomized 1:1 to receive EPIVIR 300 mg once daily or EPIVIR 150 mg twice daily, in
274 combination with zidovudine 300 mg twice daily and efavirenz 600 mg once daily. A total of
275 554 antiretroviral treatment-naive HIV-infected adults enrolled: male (79%), Caucasian (50%),
276 median age of 35 years, baseline CD4+ cell counts of 69 to 1,089 cells/mm³
277 (median = 362 cells/mm³), and median baseline plasma HIV-1 RNA of 4.66 log₁₀ copies/mL.
278 Outcomes of treatment through 48 weeks are summarized in Figure 1 and Table 3.

279

280 **Figure 1. Virologic Response Through Week 48, EPV20001*†**
281 **(Intent-to-Treat)**



282

283 * Roche AMPLICOR HIV-1 MONITOR.

284 † Responders at each visit are patients who had achieved and maintained HIV-1 RNA
285 <400 copies/mL without discontinuation by that visit.

286

287 **Table 3. Outcomes of Randomized Treatment Through 48 Weeks**
 288 **(Intent-to-Treat)**

Outcome	EPIVIR 300 mg Once Daily plus RETROVIR plus Efavirenz (n = 278)	EPIVIR 150 mg Twice Daily plus RETROVIR plus Efavirenz (n = 276)
Responder*	67%	65%
Virologic failure [†]	8%	8%
Discontinued due to clinical progression	<1%	0%
Discontinued due to adverse events	6%	12%
Discontinued due to other reasons [‡]	18%	14%

289 * Achieved confirmed plasma HIV-1 RNA <400 copies/mL and maintained through 48 weeks.

290 [†] Achieved suppression but rebounded by Week 48, discontinued due to virologic failure,
 291 insufficient viral response according to the investigator, or never suppressed through Week 48.

292 [‡] Includes consent withdrawn, lost to followup, protocol violation, data outside the study-defined
 293 schedule, and randomized but never initiated treatment.

294

295 The proportions of patients with HIV-1 RNA <50 copies/mL (via Roche Ultrasensitive assay)
 296 through Week 48 were 61% for patients receiving EPIVIR 300 mg once daily and 63% for
 297 patients receiving EPIVIR 150 mg twice daily. Median increases in CD4+ cell counts were
 298 144 cells/mm³ at Week 48 in patients receiving EPIVIR 300 mg once daily and 146 cells/mm³ for
 299 patients receiving EPIVIR 150 mg twice daily.

300 A small, randomized, open-label pilot study, EPV40001, was conducted in Thailand. A total
 301 of 159 treatment-naïve adult patients (male 32%, Asian 100%, median age 30 years, baseline
 302 median CD4+ cell count 380 cells/mm³, median plasma HIV-1 RNA 4.8 log₁₀ copies/mL) were
 303 enrolled. Two of the treatment arms in this study provided a comparison between lamivudine
 304 300 mg once daily (n = 54) and lamivudine 150 mg twice daily (n = 52), each in combination
 305 with zidovudine 300 mg twice daily and abacavir 300 mg twice daily. In intent-to-treat analyses
 306 of 48-week data, the proportions of patients with HIV-1 RNA below 400 copies/mL were 61%
 307 (33/54) in the group randomized to once-daily lamivudine and 75% (39/52) in the group
 308 randomized to receive all 3 drugs twice daily; the proportions with HIV-1 RNA below
 309 50 copies/mL were 54% (29/54) in the once-daily lamivudine group and 67% (35/52) in the
 310 all-twice-daily group; and the median increases in CD4+ cell counts were 166 cells/mm³ in the
 311 once-daily lamivudine group and 216 cells/mm³ in the all-twice-daily group.

312 **Clinical Endpoint Study in Pediatric Patients:** ACTG300 was a multicenter,
 313 randomized, double-blind study that provided for comparison of EPIVIR plus RETROVIR[®]
 314 (zidovudine) to didanosine monotherapy. A total of 471 symptomatic, HIV-infected
 315 therapy-naïve (≤56 days of antiretroviral therapy) pediatric patients were enrolled in these
 316 2 treatment arms. The median age was 2.7 years (range 6 weeks to 14 years), 58% were female,

317 and 86% were non-Caucasian. The mean baseline CD4+ cell count was 868 cells/mm³ (mean:
 318 1,060 cells/mm³ and range: 0 to 4,650 cells/mm³ for patients ≤5 years of age; mean
 319 419 cells/mm³ and range: 0 to 1,555 cells/mm³ for patients >5 years of age) and the mean
 320 baseline plasma HIV-1 RNA was 5.0 log₁₀ copies/mL. The median duration on study was
 321 10.1 months for the patients receiving EPIVIR plus RETROVIR and 9.2 months for patients
 322 receiving didanosine monotherapy. Results are summarized in Table 4.

323
 324
 325

Table 4. Number of Patients (%) Reaching a Primary Clinical Endpoint (Disease Progression or Death)

Endpoint	EPIVIR plus RETROVIR (n = 236)	Didanosine (n = 235)
HIV disease progression or death (total)	15 (6.4%)	37 (15.7%)
Physical growth failure	7 (3.0%)	6 (2.6%)
Central nervous system deterioration	4 (1.7%)	12 (5.1%)
CDC Clinical Category C	2 (0.8%)	8 (3.4%)
Death	2 (0.8%)	11 (4.7%)

326 **CONTRAINDICATIONS**

327 EPIVIR Tablets and Oral Solution are contraindicated in patients with previously
 328 demonstrated clinically significant hypersensitivity to any of the components of the products.

329 **WARNINGS**

330 **In pediatric patients with a history of prior antiretroviral nucleoside exposure, a history**
 331 **of pancreatitis, or other significant risk factors for the development of pancreatitis,**
 332 **EPIVIR should be used with caution. Treatment with EPIVIR should be stopped**
 333 **immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of**
 334 **pancreatitis occur (see ADVERSE REACTIONS).**

335 **Lactic Acidosis/Severe Hepatomegaly with Steatosis:** Lactic acidosis and severe
 336 hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside
 337 analogues alone or in combination, including lamivudine and other antiretrovirals. A majority of
 338 these cases have been in women. Obesity and prolonged nucleoside exposure may be risk
 339 factors. Particular caution should be exercised when administering EPIVIR to any patient with
 340 known risk factors for liver disease; however, cases have also been reported in patients with no
 341 known risk factors. Treatment with EPIVIR should be suspended in any patient who develops
 342 clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which
 343 may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

344 **Important Differences Among Lamivudine-Containing Products:** EPIVIR Tablets and
 345 Oral Solution contain a higher dose of the same active ingredient (lamivudine) than in
 346 EPIVIR-HBV Tablets and Oral Solution. EPIVIR-HBV was developed for patients with chronic

347 hepatitis B. The formulation and dosage of lamivudine in EPIVIR-HBV are not appropriate for
348 patients dually infected with HIV and HBV. Lamivudine has not been adequately studied for
349 treatment of chronic hepatitis B in patients dually infected with HIV and HBV. If treatment with
350 EPIVIR-HBV is prescribed for chronic hepatitis B for a patient with unrecognized or untreated
351 HIV infection, rapid emergence of HIV resistance is likely to result because of the
352 subtherapeutic dose and the inappropriateness of monotherapy HIV treatment. If a decision is
353 made to administer lamivudine to patients dually infected with HIV and HBV, EPIVIR Tablets,
354 EPIVIR Oral Solution, or COMBIVIR[®] (lamivudine/zidovudine) Tablets should be used as part
355 of an appropriate combination regimen. COMBIVIR (a fixed-dose combination tablet of
356 lamivudine and zidovudine) should not be administered concomitantly with EPIVIR,
357 EPIVIR-HBV, RETROVIR, or TRIZIVIR[®].

358 **Posttreatment Exacerbations of Hepatitis:** In clinical trials in non-HIV-infected patients
359 treated with lamivudine for chronic hepatitis B, clinical and laboratory evidence of exacerbations
360 of hepatitis have occurred after discontinuation of lamivudine. These exacerbations have been
361 detected primarily by serum ALT elevations in addition to re-emergence of HBV DNA.
362 Although most events appear to have been self-limited, fatalities have been reported in some
363 cases. Similar events have been reported from post-marketing experience after changes from
364 lamivudine-containing HIV treatment regimens to non-lamivudine-containing regimens in
365 patients infected with both HIV and HBV. The causal relationship to discontinuation of
366 lamivudine treatment is unknown. Patients should be closely monitored with both clinical and
367 laboratory followup for at least several months after stopping treatment. There is insufficient
368 evidence to determine whether re-initiation of lamivudine alters the course of posttreatment
369 exacerbations of hepatitis.

370 **PRECAUTIONS**

371 **Patients with Impaired Renal Function:** Reduction of the dosage of EPIVIR is
372 recommended for patients with impaired renal function (see CLINICAL PHARMACOLOGY
373 and DOSAGE AND ADMINISTRATION).

374 **Patients with HIV and Hepatitis B Virus Coinfection:** Safety and efficacy of lamivudine
375 have not been established for treatment of chronic hepatitis B in patients dually infected with
376 HIV and HBV. In non-HIV-infected patients treated with lamivudine for chronic hepatitis B,
377 emergence of lamivudine-resistant HBV has been detected and has been associated with
378 diminished treatment response (see EPIVIR-HBV package insert for additional information).
379 Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been
380 reported in HIV-infected patients who have received lamivudine-containing antiretroviral
381 regimens in the presence of concurrent infection with hepatitis B virus. Posttreatment
382 exacerbations of hepatitis have also been reported (see WARNINGS).

383 **Differences Between Dosing Regimens:** Trough levels of lamivudine in plasma and of
384 intracellular lamivudine triphosphate were lower with once-daily dosing than with twice-daily
385 dosing (see CLINICAL PHARMACOLOGY). The clinical significance of this observation is not

386 known.

387 **Fat Redistribution:** Redistribution/accumulation of body fat including central obesity,
388 dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast
389 enlargement, and “cushingoid appearance” have been observed in patients receiving
390 antiretroviral therapy. The mechanism and long-term consequences of these events are currently
391 unknown. A causal relationship has not been established.

392 **Information for Patients:** EPIVIR is not a cure for HIV infection and patients may continue
393 to experience illnesses associated with HIV infection, including opportunistic infections. Patients
394 should remain under the care of a physician when using EPIVIR. Patients should be advised that
395 the use of EPIVIR has not been shown to reduce the risk of transmission of HIV to others
396 through sexual contact or blood contamination.

397 Patients should be advised that EPIVIR Tablets and Oral Solution contain a higher dose of the
398 same active ingredient (lamivudine) as EPIVIR-HBV Tablets and Oral Solution. If a decision is
399 made to include lamivudine in the HIV treatment regimen of a patient dually infected with HIV
400 and HBV, the formulation and dosage of lamivudine in EPIVIR (not EPIVIR-HBV) should be
401 used.

402 Patients co-infected with HIV and HBV should be informed that deterioration of liver disease
403 has occurred in some cases when treatment with lamivudine was discontinued. Patients should be
404 advised to discuss any changes in regimen with their physician.

405 Patients should be advised that the long-term effects of EPIVIR are unknown at this time.

406 EPIVIR Tablets and Oral Solution are for oral ingestion only.

407 Patients should be advised of the importance of taking EPIVIR with combination therapy on a
408 regular dosing schedule and to avoid missing doses.

409 Parents or guardians should be advised to monitor pediatric patients for signs and symptoms
410 of pancreatitis.

411 Patients should be informed that redistribution or accumulation of body fat may occur in
412 patients receiving antiretroviral therapy and that the cause and long-term health effects of these
413 conditions are not known at this time.

414 Diabetic patients should be advised that each 15-mL dose of EPIVIR Oral Solution contains
415 3 grams of sucrose.

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

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

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

428 **Carcinogenesis, Mutagenesis, and Impairment of Fertility:** Long-term carcinogenicity
429 studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at
430 exposures up to 10 times (mice) and 58 times (rats) those observed in humans at the
431 recommended therapeutic dose for HIV infection. Lamivudine was not active in a microbial
432 mutagenicity screen or an in vitro cell transformation assay, but showed weak in vitro mutagenic
433 activity in a cytogenetic assay using cultured human lymphocytes and in the mouse lymphoma
434 assay. However, lamivudine showed no evidence of in vivo genotoxic activity in the rat at oral
435 doses of up to 2,000 mg/kg, producing plasma levels of 35 to 45 times those in humans at the
436 recommended dose for HIV infection. In a study of reproductive performance, lamivudine
437 administered to rats at doses up to 4,000 mg/kg/day, producing plasma levels 47 to 70 times
438 those in humans, revealed no evidence of impaired fertility and no effect on the survival, growth,
439 and development to weaning of the offspring.

440 **Pregnancy:** Pregnancy Category C. Reproduction studies have been performed in rats and
441 rabbits at orally administered doses up to 4,000 mg/kg/day and 1,000 mg/kg/day, respectively,
442 producing plasma levels up to approximately 35 times that for the adult HIV dose. No evidence
443 of teratogenicity due to lamivudine was observed. Evidence of early embryoletality was seen in
444 the rabbit at exposure levels similar to those observed in humans, but there was no indication of
445 this effect in the rat at exposure levels up to 35 times that in humans. Studies in pregnant rats and
446 rabbits showed that lamivudine is transferred to the fetus through the placenta.

447 In 2 clinical studies conducted in South Africa, pharmacokinetic measurements were
448 performed on samples from pregnant women who received lamivudine beginning at week 38 of
449 gestation (10 women who received 150 mg twice daily in combination with zidovudine and 10
450 who received lamivudine 300 mg twice daily without other antiretrovirals) or beginning at week
451 36 of gestation (16 women who received lamivudine 150 mg twice daily in combination with
452 zidovudine). These studies were not designed or powered to provide efficacy information.
453 Lamivudine pharmacokinetics in the pregnant women were similar to those obtained following
454 birth and in non-pregnant adults. Lamivudine concentrations were generally similar in maternal,
455 neonatal, and cord serum samples. In a subset of subjects from whom amniotic fluid specimens
456 were obtained following natural rupture of membranes, amniotic fluid concentrations of
457 lamivudine ranged from 1.2 to 2.5 mcg/mL (150 mg twice daily) and 2.1 to 5.2 mcg/mL (300 mg
458 twice daily) and were typically greater than 2 times the maternal serum levels. See the
459 ADVERSE REACTIONS section for the limited late-pregnancy safety information available
460 from these studies. Lamivudine should be used during pregnancy only if the potential benefits
461 outweigh the risks.

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

465 **Nursing Mothers: The Centers for Disease Control and Prevention recommend that**
466 **HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission**
467 **of HIV infection.**

468 A study in lactating rats administered 45 mg/kg of lamivudine showed that lamivudine
469 concentrations in milk were slightly greater than those in plasma. Lamivudine is also excreted in
470 human milk. Samples of breast milk obtained from 20 mothers receiving lamivudine
471 monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice daily and
472 300 mg zidovudine twice daily) had measurable concentrations of lamivudine.

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

476 **Pediatric Use: HIV:** Limited, uncontrolled pharmacokinetic and safety data are available from
477 administration of lamivudine (and zidovudine) to 36 infants up to 1 week of age in 2 studies in
478 South Africa. In these studies, lamivudine clearance was substantially reduced in 1-week-old
479 neonates relative to pediatric patients (>3 months of age) studied previously. There is insufficient
480 information to establish the time course of changes in clearance between the immediate neonatal
481 period and the age-ranges >3 months old. See the ADVERSE REACTIONS section for the
482 limited safety information available from these studies.

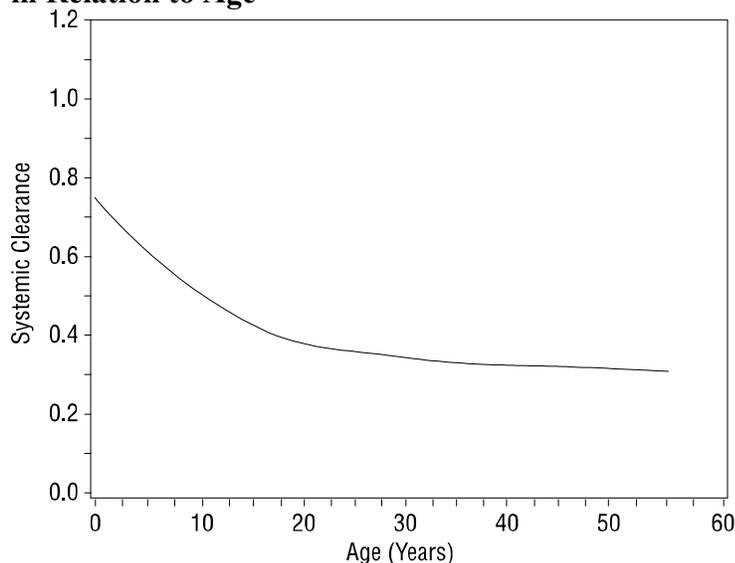
483 The safety and effectiveness of twice-daily EPIVIR in combination with other antiretroviral
484 agents have been established in pediatric patients 3 months of age and older.

485 In Study A2002, pharmacokinetic properties of lamivudine were assessed in a subset of
486 57 HIV-infected pediatric patients (age range: 4.8 months to 16 years, weight range: 5 to 66 kg)
487 after oral and IV administration of 1, 2, 4, 8, 12, and 20 mg/kg/day. In the 9 infants and children
488 (range: 5 months to 12 years of age) receiving oral solution 4 mg/kg twice daily (the usual
489 recommended pediatric dose), absolute bioavailability was $66\% \pm 26\%$ (mean \pm SD), which was
490 less than the $86\% \pm 16\%$ (mean \pm SD) observed in adults. The mechanism for the diminished
491 absolute bioavailability of lamivudine in infants and children is unknown.

492 Systemic clearance decreased with increasing age in pediatric patients, as shown in Figure 2.

493

494 **Figure 2. Systemic Clearance (L/hr•kg) of Lamivudine**
495 **in Relation to Age**



496
497

498 After oral administration of lamivudine 4 mg/kg twice daily to 11 pediatric patients ranging
499 from 4 months to 14 years of age, C_{max} was 1.1 ± 0.6 mcg/mL and half-life was 2.0 ± 0.6 hours.
500 (In adults with similar blood sampling, the half-life was 3.7 ± 1 hours.) Total exposure to
501 lamivudine, as reflected by mean AUC values, was comparable between pediatric patients
502 receiving an 8-mg/kg/day dose and adults receiving a 4-mg/kg/day dose.

503 Distribution of lamivudine into cerebrospinal fluid (CSF) was assessed in 38 pediatric patients
504 after multiple oral dosing with lamivudine. CSF samples were collected between 2 and 4 hours
505 postdose. At the dose of 8 mg/kg/day, CSF lamivudine concentrations in 8 patients ranged from
506 5.6% to 30.9% (mean \pm SD of $14.2\% \pm 7.9\%$) of the concentration in a simultaneous serum
507 sample, with CSF lamivudine concentrations ranging from 0.04 to 0.3 mcg/mL.

508 The effect of renal impairment on lamivudine pharmacokinetics in pediatric patients is not
509 known.

510 The safety and pharmacokinetic properties of EPIVIR in combination with antiretroviral
511 agents other than zidovudine have not been established in pediatric patients.

512 See INDICATIONS AND USAGE: Description of Clinical Studies, CLINICAL
513 PHARMACOLOGY, WARNINGS, ADVERSE REACTIONS, and DOSAGE AND
514 ADMINISTRATION.

515 **HBV:** See the complete prescribing information for EPIVIR-HBV Tablets and Oral Solution
516 for additional information on the pharmacokinetics of lamivudine in HBV-infected children.

517 **Geriatric Use:** Clinical studies of EPIVIR did not include sufficient numbers of subjects aged
518 65 and over to determine whether they respond differently from younger subjects. In general,
519 dose selection for an elderly patient should be cautious, reflecting the greater frequency of
520 decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.
521 In particular, because lamivudine is substantially excreted by the kidney and elderly patients are

522 more likely to have decreased renal function, renal function should be monitored and dosage
523 adjustments should be made accordingly (see PRECAUTIONS: Patients with Impaired Renal
524 Function and DOSAGE AND ADMINISTRATION).

525 **ADVERSE REACTIONS**

526 **Clinical Trials in HIV: Adults:** Selected clinical adverse events with a $\geq 5\%$ frequency during
527 therapy with EPIVIR 150 mg twice daily plus RETROVIR 200 mg 3 times daily compared with
528 zidovudine are listed in Table 5.
529

530 **Table 5. Selected Clinical Adverse Events (≥5% Frequency) in Four Controlled Clinical**
 531 **Trials (A3001, A3002, B3001, B3002)**

Adverse Event	EPIVIR 150 mg Twice Daily plus RETROVIR (n = 251)	RETROVIR* (n = 230)
Body as a whole		
Headache	35%	27%
Malaise & fatigue	27%	23%
Fever or chills	10%	12%
Digestive		
Nausea	33%	29%
Diarrhea	18%	22%
Nausea & vomiting	13%	12%
Anorexia and/or decreased appetite	10%	7%
Abdominal pain	9%	11%
Abdominal cramps	6%	3%
Dyspepsia	5%	5%
Nervous system		
Neuropathy	12%	10%
Insomnia & other sleep disorders	11%	7%
Dizziness	10%	4%
Depressive disorders	9%	4%
Respiratory		
Nasal signs & symptoms	20%	11%
Cough	18%	13%
Skin		
Skin rashes	9%	6%
Musculoskeletal		
Musculoskeletal pain	12%	10%
Myalgia	8%	6%
Arthralgia	5%	5%

532 *Either zidovudine monotherapy or zidovudine in combination with zalcitabine.
 533

534 The types and frequencies of clinical adverse events reported in patients receiving
 535 EPIVIR 300 mg once daily or EPIVIR 150 mg twice daily (in 3-drug combination
 536 regimens in EPV20001 and EPV40001) were similar. The most common adverse events
 537 in both treatment groups were nausea, dizziness, fatigue and/or malaise, headache,
 538 dreams, insomnia and other sleep disorders, and skin rash.

539 Pancreatitis was observed in 9 of the 2,613 adult patients (0.3%) who received EPIVIR in the
 540 controlled clinical trials EPV20001, NUCA3001, NUCB3001, NUCA3002, NUCB3002, and
 541 B3007.

542 Selected laboratory abnormalities observed during therapy are summarized in Table 6.
 543

544 **Table 6. Frequencies of Selected Laboratory Abnormalities in Adults in Four 24-Week**
 545 **Surrogate Endpoint Studies (A3001, A3002, B3001, B3002) and a Clinical Endpoint Study**
 546 **(B3007)**

Test (Threshold Level)	24-Week Surrogate Endpoint Studies*		Clinical Endpoint Study*	
	EPIVIR plus RETROVIR	RETROVIR [†]	EPIVIR plus Current Therapy	Placebo plus Current Therapy [‡]
Absolute neutrophil count ($<750/\text{mm}^3$)	7.2%	5.4%	15%	13%
Hemoglobin (<8.0 g/dL)	2.9%	1.8%	2.2%	3.4%
Platelets ($<50,000/\text{mm}^3$)	0.4%	1.3%	2.8%	3.8%
ALT (>5.0 x ULN)	3.7%	3.6%	3.8%	1.9%
AST (>5.0 x ULN)	1.7%	1.8%	4.0%	2.1%
Bilirubin (>2.5 x ULN)	0.8%	0.4%	ND	ND
Amylase (>2.0 x ULN)	4.2%	1.5%	2.2%	1.1%

547 *The median duration on study was 12 months.

548 [†] Either zidovudine monotherapy or zidovudine in combination with zalcitabine.

549 [‡]Current therapy was either zidovudine, zidovudine plus didanosine, or zidovudine plus
 550 zalcitabine.

551 ULN = Upper limit of normal.

552 ND = Not done.
 553

554 In small, uncontrolled studies in which pregnant women were given lamivudine alone or in
 555 combination with zidovudine beginning in the last few weeks of pregnancy (see
 556 PRECAUTIONS: Pregnancy), reported adverse events included anemia, urinary tract infections,
 557 and complications of labor and delivery. In postmarketing experience, liver function
 558 abnormalities and pancreatitis have been reported in women who received lamivudine in
 559 combination with other antiretroviral drugs during pregnancy. It is not known whether risks of

560 adverse events associated with lamivudine are altered in pregnant women compared to other
 561 HIV-infected patients.

562 The frequencies of selected laboratory abnormalities reported in patients receiving EPIVIR
 563 300 mg once daily or EPIVIR 150 mg twice daily (in 3-drug combination regimens in
 564 EPV20001 and EPV40001) were similar.

565 **Pediatric Patients:** Selected clinical adverse events and physical findings with a $\geq 5\%$
 566 frequency during therapy with EPIVIR 4 mg/kg twice daily plus RETROVIR 160 mg/m² 3 times
 567 daily compared with didanosine in therapy-naive (≤ 56 days of antiretroviral therapy) pediatric
 568 patients are listed in Table 7.

570 **Table 7. Selected Clinical Adverse Events and Physical Findings ($\geq 5\%$ Frequency)**
 571 **in Pediatric Patients in Study ACTG300**

Adverse Event	EPIVIR plus RETROVIR (n = 236)	Didanosine (n = 235)
Body as a whole		
Fever	25%	32%
Digestive		
Hepatomegaly	11%	11%
Nausea & vomiting	8%	7%
Diarrhea	8%	6%
Stomatitis	6%	12%
Splenomegaly	5%	8%
Respiratory		
Cough	15%	18%
Abnormal breath sounds/wheezing	7%	9%
Ear, Nose, and Throat		
Signs or symptoms of ears*	7%	6%
Nasal discharge or congestion	8%	11%
Other		
Skin rashes	12%	14%
Lymphadenopathy	9%	11%

572 *Includes pain, discharge, erythema, or swelling of an ear.

573
 574 Selected laboratory abnormalities experienced by therapy-naive (≤ 56 days of antiretroviral
 575 therapy) pediatric patients are listed in Table 8.

576

577 **Table 8. Frequencies of Selected Laboratory Abnormalities in Pediatric Patients in Study**
 578 **ACTG300**

Test (Threshold Level)	EPIVIR plus RETROVIR	Didanosine
Absolute neutrophil count (<400/mm ³)	8%	3%
Hemoglobin (<7.0 g/dL)	4%	2%
Platelets (<50,000/mm ³)	1%	3%
ALT (>10 x ULN)	1%	3%
AST (>10 x ULN)	2%	4%
Lipase (>2.5 x ULN)	3%	3%
Total Amylase (>2.5 x ULN)	3%	3%

579 ULN = Upper limit of normal.

580

581 Pancreatitis, which has been fatal in some cases, has been observed in antiretroviral
 582 nucleoside-experienced pediatric patients receiving EPIVIR alone or in combination with other
 583 antiretroviral agents. In an open-label dose-escalation study (A2002), 14 patients (14%)
 584 developed pancreatitis while receiving monotherapy with EPIVIR. Three of these patients died
 585 of complications of pancreatitis. In a second open-label study (A2005), 12 patients (18%)
 586 developed pancreatitis. In Study ACTG300, pancreatitis was not observed in 236 patients
 587 randomized to EPIVIR plus RETROVIR. Pancreatitis was observed in 1 patient in this study
 588 who received open-label EPIVIR in combination with RETROVIR and ritonavir following
 589 discontinuation of didanosine monotherapy.

590 Paresthesias and peripheral neuropathies were reported in 15 patients (15%) in Study A2002,
 591 6 patients (9%) in Study A2005, and 2 patients (<1%) in Study ACTG300.

592 Limited short-term safety information is available from 2 small, uncontrolled studies in South
 593 Africa in neonates receiving lamivudine with or without zidovudine for the first week of life
 594 following maternal treatment starting at week 38 or 36 of gestation (see PRECAUTIONS:
 595 Pediatric Use). Adverse events reported in these neonates included increased liver function tests,
 596 anemia, diarrhea, electrolyte disturbances, hypoglycemia, jaundice and hepatomegaly, rash,
 597 respiratory infections, sepsis, and syphilis; 3 neonates died (1 from gastroenteritis with acidosis
 598 and convulsions, 1 from traumatic injury, and 1 from unknown causes). Two other nonfatal
 599 gastroenteritis or diarrhea cases were reported, including 1 with convulsions; 1 infant had
 600 transient renal insufficiency associated with dehydration. The absence of control groups further
 601 limits assessments of causality, but it should be assumed that perinatally-exposed infants may be
 602 at risk for adverse events comparable to those reported in pediatric and adult HIV-infected
 603 patients treated with lamivudine-containing combination regimens. Long-term effects of in utero
 604 and infant lamivudine exposure are not known.

605 **Lamivudine in Patients with Chronic Hepatitis B:** Clinical trials in chronic hepatitis B
 606 used a lower dose of lamivudine (100 mg daily) than the dose used to treat HIV. The most

607 frequent adverse events with lamivudine versus placebo were ear, nose, and throat infections
608 (25% versus 21%); malaise and fatigue (24% versus 28%); and headache (21% versus 21%),
609 respectively. The most frequent laboratory abnormalities reported with lamivudine were elevated
610 ALT, elevated serum lipase, elevated CPK, and posttreatment elevations of liver function tests.
611 Emergence of HBV viral mutants during lamivudine treatment, associated with reduced drug
612 susceptibility and diminished treatment response, was also reported (also see WARNINGS and
613 PRECAUTIONS). Please see the complete prescribing information for EPIVIR-HBV Tablets
614 and Oral Solution for more information.

615 **Observed During Clinical Practice:** In addition to adverse events reported from clinical
616 trials, the following events have been identified during post-approval use of lamivudine. Because
617 they are reported voluntarily from a population of unknown size, estimates of frequency cannot
618 be made. These events have been chosen for inclusion due to a combination of their seriousness,
619 frequency of reporting, or potential causal connection to lamivudine.

620 **Body as a Whole:** Redistribution/accumulation of body fat (see PRECAUTIONS: Fat
621 Redistribution).

622 **Digestive:** Stomatitis.

623 **Endocrine and Metabolic:** Hyperglycemia.

624 **General:** Weakness.

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

627 **Hepatic and Pancreatic:** Lactic acidosis and hepatic steatosis, pancreatitis, posttreatment
628 exacerbation of hepatitis B (see WARNINGS and PRECAUTIONS).

629 **Hypersensitivity:** Anaphylaxis, urticaria.

630 **Musculoskeletal:** Muscle weakness, CPK elevation, rhabdomyolysis.

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

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

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

634 OVERDOSAGE

635 There is no known antidote for EPIVIR. One case of an adult ingesting 6 g of EPIVIR was
636 reported; there were no clinical signs or symptoms noted and hematologic tests remained normal.
637 Two cases of pediatric overdose were reported in ACTG300. One case was a single dose of
638 7 mg/kg of EPIVIR; the second case involved use of 5 mg/kg of EPIVIR twice daily for 30 days.
639 There were no clinical signs or symptoms noted in either case. It is not known whether
640 lamivudine can be removed by peritoneal dialysis or hemodialysis. If overdose occurs, the
641 patient should be monitored, and standard supportive treatment applied as required.

642 DOSAGE AND ADMINISTRATION

643 **Adults:** The recommended oral dose of EPIVIR for adults is 300 mg daily, administered as
644 either 150 mg twice daily or 300 mg once daily, in combination with other antiretroviral agents
645 (see DESCRIPTION OF CLINICAL STUDIES, PRECAUTIONS, MICROBIOLOGY, and

646 CLINICAL PHARMACOLOGY). If lamivudine is administered to a patient dually infected with
647 HIV and HBV, the dosage indicated for HIV therapy should be used as part of an appropriate
648 combination regimen (see WARNINGS).

649 **Pediatric Patients: Infants/Children/Adolescents:** The recommended oral dose of
650 EPIVIR for HIV-infected pediatric patients 3 months up to 16 years of age is 4 mg/kg twice
651 daily (up to a maximum of 150 mg twice a day), administered in combination with other
652 antiretroviral agents.

653 **Dose Adjustment:** It is recommended that doses of EPIVIR be adjusted in accordance with
654 renal function (see Table 9) (see CLINICAL PHARMACOLOGY).

655
656 **Table 9. Adjustment of Dosage of EPIVIR in Adults and Adolescents in Accordance with**
657 **Creatinine Clearance**

Creatinine Clearance (mL/min)	Recommended Dosage of EPIVIR
≥50	150 mg twice daily or 300 mg once daily
30-49	150 mg once daily
15-29	150 mg first dose, then 100 mg once daily
5-14	150 mg first dose, then 50 mg once daily
<5	50 mg first dose, then 25 mg once daily

658
659 Insufficient data are available to recommend a dosage of EPIVIR in patients undergoing
660 dialysis. Although there are insufficient data to recommend a specific dose adjustment of
661 EPIVIR in pediatric patients with renal impairment, a reduction in the dose and/or an increase in
662 the dosing interval should be considered.

663 HOW SUPPLIED

664 EPIVIR Tablets, 150 mg, are white, modified diamond-shaped, film-coated tablets engraved
665 with “GX CJ7” on one side and plain on the reverse side.

666 Bottle of 60 tablets (NDC 0173-0470-01) with child-resistant closure.

667 EPIVIR Tablets, 300 mg, are gray, modified diamond-shaped, film-coated tablets engraved
668 with “GX EJ7” on one side and plain on the reverse side.

669 Bottle of 30 tablets (NDC 0173-0714-00) with child-resistant closure.

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

672 EPIVIR Oral Solution, a clear, colorless to pale yellow, strawberry-banana flavored liquid,
673 contains 10 mg of lamivudine in each 1 mL in plastic bottles of 240 mL (NDC 0173-0471-00)
674 with child-resistant closures. This product does not require reconstitution.

675 **Store in tightly closed bottles at 25°C (77°F) [see USP Controlled Room Temperature].**

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GlaxoSmithKline

678

679 GlaxoSmithKline

680 Research Triangle Park, NC 27709

681

682 Manufactured under agreement from

683 **Shire Pharmaceuticals Group plc**

684 Basingstoke, UK

685

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