

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

EPIVIR (lamivudine) Tablets and Oral Solution
Initial U.S. Approval: 1995

WARNING: LACTIC ACIDOSIS, POSTTREATMENT EXACERBATIONS OF HEPATITIS B IN CO-INFECTED PATIENTS, DIFFERENT FORMULATIONS OF EPIVIR

See full prescribing information for complete boxed warning

- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur. (5.1)
- Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued EPIVIR. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.2)
- Patients with HIV-1 infection should receive only dosage forms of EPIVIR appropriate for treatment of HIV-1. (5.2)

RECENT MAJOR CHANGES

Dosage and Administration, Pediatric Patients (2.2) February 2008

INDICATIONS AND USAGE

EPIVIR is a nucleoside analogue reverse transcriptase inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. Limitation of Use: The dosage of this product is for HIV-1 and not for HBV. (1)

DOSAGE AND ADMINISTRATION

- Adults and adolescents >16 years of age: 300 mg daily, administered as either 150 mg twice daily or 300 mg once daily. (2.1)
- Pediatric patients 3 months up to 16 years of age: Dosage should be based on body weight. (2.2)
- Patients With Renal Impairment: Doses of EPIVIR must be adjusted in accordance with renal function. (2.3)

DOSAGE FORMS AND STRENGTHS

- Tablets: 300 mg (3)
- Tablets: Scored 150 mg (3)
- Oral Solution: 10 mg/mL (3)

CONTRAINDICATIONS

EPIVIR Tablets and Oral Solution are contraindicated in patients with previously demonstrated clinically significant hypersensitivity (e.g., anaphylaxis) to any of the components of the products. (4)

WARNINGS AND PRECAUTIONS

- Lactic acidosis and severe hepatomegaly with steatosis: Reported with the use of nucleoside analogues. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur. (5.1)
- Severe acute exacerbations of hepatitis: Reported in patients who are co-infected with hepatitis B virus and HIV-1 and discontinued EPIVIR. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.2)
- Patients with HIV-1 infection should receive only dosage forms of EPIVIR appropriate for treatment of HIV-1. (5.2)
- Co-infected HIV-1/HBV Patients: Emergence of lamivudine-resistant HBV variants associated with lamivudine-containing antiretroviral regimens has been reported. (5.2)
- Emtricitabine should not be administered concomitantly with lamivudine-containing products. (5.3)
- Hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving interferon and ribavirin-based regimens. Monitor for treatment-associated toxicities. Discontinue EPIVIR as medically appropriate and consider dose reduction or discontinuation of interferon alfa, ribavirin, or both. (5.4)
- Pancreatitis: Use with caution in pediatric patients with a history of pancreatitis or other significant risk factors for pancreatitis. Discontinue treatment as clinically appropriate. (5.5)
- Immune reconstitution syndrome (5.6) and redistribution/accumulation of body fat (5.7) have been reported in patients treated with combination antiretroviral therapy.

ADVERSE REACTIONS

- The most common reported adverse reactions (incidence $\geq 15\%$) in adults were headache, nausea, malaise and fatigue, nasal signs and symptoms, diarrhea, and cough. (6.1)
- The most common reported adverse reactions (incidence $\geq 15\%$) in pediatric patients were fever and cough. (6.1)

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

DRUG INTERACTIONS

Zalcitabine is not recommended for use in combination with EPIVIR. (7.2)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Physicians are encouraged to register patients in the Antiretroviral Pregnancy Registry by calling 1-800-258-4263. (8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: February 2008

EPV:1PI

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1

2 **FULL PRESCRIBING INFORMATION**

3 **WARNING: RISK OF LACTIC ACIDOSIS, EXACERBATIONS OF HEPATITIS B IN**
4 **CO-INFECTED PATIENTS UPON DISCONTINUATION OF EPIVIR[®], DIFFERENT**
5 **FORMULATIONS OF EPIVIR.**

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

11 Severe acute exacerbations of hepatitis B have been reported in patients who are
12 co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and
13 have discontinued EPIVIR. Hepatic function should be monitored closely with both clinical
14 and laboratory follow-up for at least several months in patients who discontinue EPIVIR
15 and are co-infected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B
16 therapy may be warranted [see Warnings and Precautions (5.2)].

17 EPIVIR Tablets and Oral Solution (used to treat HIV-1 infection) contain a higher
18 dose of the active ingredient (lamivudine) than EPIVIR-HBV[®] Tablets and Oral Solution
19 (used to treat chronic HBV infection). Patients with HIV-1 infection should receive only
20 dosage forms appropriate for treatment of HIV-1 [see Warnings and Precautions (5.2)].

21 **1 INDICATIONS AND USAGE**

22 EPIVIR is a nucleoside analogue indicated in combination with other antiretroviral
23 agents for the treatment of human immunodeficiency virus (HIV-1) infection. Limitation of use:
24 The dosage of this product is for HIV-1 and not for HBV.

25 **2 DOSAGE AND ADMINISTRATION**

26 **2.1 Adults and Adolescents >16 years of age**

27 The recommended oral dose of EPIVIR in HIV-1-infected adults and adolescents
28 >16 years of age is 300 mg daily, administered as either 150 mg twice daily or 300 mg once
29 daily, in combination with other antiretroviral agents. If lamivudine is administered to a patient
30 infected with HIV-1 and HBV, the dosage indicated for HIV-1 therapy should be used as part of
31 an appropriate combination regimen [see Warnings and Precautions (5.2)].

32 **2.2 Pediatric Patients**

33 The recommended oral dose of EPIVIR Oral Solution in HIV-1-infected pediatric
34 patients 3 months to 16 years of age is 4 mg/kg twice daily (up to a maximum of 150 mg twice a
35 day), administered in combination with other antiretroviral agents.

36 EPIVIR is also available as a scored tablet for HIV-1-infected pediatric patients who
37 weigh ≥ 14 kg for whom a solid dosage form is appropriate. Before prescribing EPIVIR Tablets,

38 children should be assessed for the ability to swallow tablets. If a child is unable to reliably
 39 swallow EPIVIR Tablets, the oral solution formulation should be prescribed. The recommended
 40 oral dosage of EPIVIR Tablets for HIV-1-infected pediatric patients is presented in Table 1.
 41

42 **Table 1. Dosing Recommendations for EPIVIR Tablets in Pediatric Patients**

Weight (kg)	Dosage Regimen Using Scored 150 mg Tablet		Total Daily Dose
	AM Dose	PM Dose	
14 to 21	½ tablet (75 mg)	½ tablet (75 mg)	150 mg
>21 to <30	½ tablet (75 mg) ^a	1 tablet (150 mg)	225 mg
≥30	1 tablet (150 mg)	1 tablet (150 mg)	300 mg

43
 44 **2.3 Patients With Renal Impairment**

45 Dosing of EPIVIR is adjusted in accordance with renal function. Dosage adjustments are
 46 listed in Table 2 [see *Clinical Pharmacology (12.3)*].
 47

48 **Table 2. Adjustment of Dosage of EPIVIR in Adults and Adolescents (≥30 kg) in**
 49 **Accordance With 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

50
 51 No additional dosing of EPIVIR is required after routine (4-hour) hemodialysis or
 52 peritoneal dialysis.

53 Although there are insufficient data to recommend a specific dose adjustment of EPIVIR
 54 in pediatric patients with renal impairment, a reduction in the dose and/or an increase in the
 55 dosing interval should be considered.

56 **3 DOSAGE FORMS AND STRENGTHS**

57 • **EPIVIR Scored Tablets**

58 150 mg, are white, diamond-shaped, scored, film-coated tablets debossed with "GX CJ7"
 59 on both sides.

60 • **EPIVIR Tablets**

61 300 mg, are gray, modified diamond-shaped, film-coated tablets engraved with "GX EJ7"
 62 on one side and plain on the reverse side.

63 • **EPIVIR Oral Solution**

64 A clear, colorless to pale yellow, strawberry-banana flavored liquid, contains 10 mg of

65 lamivudine per 1 mL.

66 **4 CONTRAINDICATIONS**

67 EPIVIR Tablets and Oral Solution are contraindicated in patients with previously
68 demonstrated clinically significant hypersensitivity (e.g., anaphylaxis) to any of the components
69 of the products.

70 **5 WARNINGS AND PRECAUTIONS**

71 **5.1 Lactic Acidosis/Severe Hepatomegaly With Steatosis**

72 Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been
73 reported with the use of nucleoside analogues alone or in combination, including lamivudine and
74 other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged
75 nucleoside exposure may be risk factors. Particular caution should be exercised when
76 administering EPIVIR to any patient with known risk factors for liver disease; however, cases
77 have also been reported in patients with no known risk factors. Treatment with EPIVIR should
78 be suspended in any patient who develops clinical or laboratory findings suggestive of lactic
79 acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in
80 the absence of marked transaminase elevations).

81 **5.2 Patients With HIV-1 and Hepatitis B Virus Co-infection**

82 Posttreatment Exacerbations of Hepatitis: In clinical trials in non-HIV-1-infected
83 patients treated with lamivudine for chronic hepatitis B, clinical and laboratory evidence of
84 exacerbations of hepatitis have occurred after discontinuation of lamivudine. These
85 exacerbations have been detected primarily by serum ALT elevations in addition to
86 re-emergence of HBV DNA. Although most events appear to have been self-limited, fatalities
87 have been reported in some cases. Similar events have been reported from postmarketing
88 experience after changes from lamivudine-containing HIV-1² treatment regimens to
89 non-lamivudine-containing regimens in patients infected with both HIV-1 and HBV. The causal
90 relationship to discontinuation of lamivudine treatment is unknown. Patients should be closely
91 monitored with both clinical and laboratory followup for at least several months after stopping
92 treatment. There is insufficient evidence to determine whether re-initiation of lamivudine alters
93 the course of posttreatment exacerbations of hepatitis.

94 Important Differences Among Lamivudine-Containing Products: EPIVIR Tablets
95 and Oral Solution contain a higher dose of the same active ingredient (lamivudine) than
96 EPIVIR-HBV Tablets and EPIVIR-HBV Oral Solution. EPIVIR-HBV was developed for
97 patients with chronic hepatitis B. The formulation and dosage of lamivudine in EPIVIR-HBV are
98 not appropriate for patients co-infected with HIV-1 and HBV. Safety and efficacy of lamivudine
99 have not been established for treatment of chronic hepatitis B in patients co-infected with HIV-1
100 and HBV. If treatment with EPIVIR-HBV is prescribed for chronic hepatitis B for a patient with
101 unrecognized or untreated HIV-1 infection, rapid emergence of HIV-1 resistance is likely to
102 result because of the subtherapeutic dose and the inappropriateness of monotherapy HIV-1
103 treatment. If a decision is made to administer lamivudine to patients co-infected with HIV-1 and

104 HBV, EPIVIR Tablets, EPIVIR Oral Solution, COMBIVIR[®] (lamivudine/zidovudine) Tablets,
105 EPZICOM[®] (abacavir sulfate and lamivudine) Tablets, or TRIZIVIR[®] (abacavir sulfate,
106 lamivudine, and zidovudine) Tablets should be used as part of an appropriate combination
107 regimen.

108 Emergence of Lamivudine-Resistant HBV: In non-HIV-1-infected patients treated
109 with lamivudine for chronic hepatitis B, emergence of lamivudine-resistant HBV has been
110 detected and has been associated with diminished treatment response (see full prescribing
111 information for EPIVIR-HBV for additional information). Emergence of hepatitis B virus
112 variants associated with resistance to lamivudine has also been reported in HIV-1-infected
113 patients who have received lamivudine-containing antiretroviral regimens in the presence of
114 concurrent infection with hepatitis B virus.

115 **5.3 Use With Other Lamivudine- and Emtricitabine-Containing Products**

116 EPIVIR should not be administered concomitantly with other lamivudine-containing
117 products including EPIVIR-HBV Tablets, EPIVIR Oral Solution, COMBIVIR
118 (lamivudine/zidovudine) Tablets, EPZICOM (abacavir sulfate and lamivudine) Tablets, or
119 TRIZIVIR (abacavir sulfate, lamivudine, and zidovudine) or emtricitabine-containing products,
120 including ATRIPLA[™] (efavirenz, emtricitabine, and tenofovir), EMTRIVA[®] (emtricitabine), or
121 TRUVADA[®] (emtricitabine and tenofovir).

122 **5.4 Use With Interferon- and Ribavirin-Based Regimens**

123 In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine
124 nucleoside analogues such as lamivudine. Although no evidence of a pharmacokinetic or
125 pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when
126 ribavirin was coadministered with lamivudine in HIV-1/HCV co-infected patients [*see Clinical*
127 *Pharmacology (12.3)*], hepatic decompensation (some fatal) has occurred in HIV-1/HCV
128 co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa
129 with or without ribavirin. Patients receiving interferon alfa with or without ribavirin and EPIVIR
130 should be closely monitored for treatment-associated toxicities, especially hepatic
131 decompensation. Discontinuation of EPIVIR should be considered as medically appropriate.
132 Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered
133 if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Childs
134 Pugh >6). See the complete prescribing information for interferon and ribavirin.

135 **5.5 Pancreatitis**

136 In pediatric patients with a history of prior antiretroviral nucleoside exposure, a history of
137 pancreatitis, or other significant risk factors for the development of pancreatitis, EPIVIR should
138 be used with caution. Treatment with EPIVIR should be stopped immediately if clinical signs,
139 symptoms, or laboratory abnormalities suggestive of pancreatitis occur [*see Adverse Reactions*
140 *(6.1)*].

141 **5.6 Immune Reconstitution Syndrome**

142 Immune reconstitution syndrome has been reported in patients treated with combination
143 antiretroviral therapy, including EPIVIR. During the initial phase of combination antiretroviral

144 treatment, patients whose immune system responds may develop an inflammatory response to
145 indolent or residual opportunistic infections (such as *Mycobacterium avium* infection,
146 cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may
147 necessitate further evaluation and treatment.

148 **5.7 Fat Redistribution**

149 Redistribution/accumulation of body fat including central obesity, dorsocervical fat
150 enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and
151 “cushingoid appearance” have been observed in patients receiving antiretroviral therapy. The
152 mechanism and long-term consequences of these events are currently unknown. A causal
153 relationship has not been established.

154 **6 ADVERSE REACTIONS**

155 **6.1 Clinical Trials Experience**

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

- 158 • Lactic acidosis and severe hepatomegaly with steatosis [*see Boxed Warning, Warnings and*
159 *Precautions (5.1)*].
- 160 • Severe acute exacerbations of hepatitis B [*see Boxed Warning, Warnings and Precautions*
161 *(5.2)*].
- 162 • Hepatic decompensation in patients co-infected with HIV-1 and Hepatitis C [*see Warnings*
163 *and Precautions (5.4)*].
- 164 • Pancreatitis [*see Warnings and Precautions (5.5)*].

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

168 Adults - Clinical Trials in HIV-1: The safety profile of EPIVIR in adults is primarily
169 based on 3,568 HIV-1-infected patients in 7 clinical trials.

170 The most common adverse reactions are headache, nausea, malaise, fatigue, nasal signs
171 and symptoms, diarrhea and cough.

172 Selected clinical adverse reactions of in $\geq 5\%$ of patients during therapy with EPIVIR
173 150 mg twice daily plus RETROVIR[®] 200 mg 3 times daily for up to 24 weeks are listed in
174 Table 3.

175 **Table 3. Selected Clinical Adverse Reactions (≥5% Frequency) in Four Controlled Clinical**
 176 **Trials (NUCA3001, NUCA3002, NUCB3001, NUCB3002)**

Adverse Reaction	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%

177 *Either zidovudine monotherapy or zidovudine in combination with zalcitabine.

178
 179 *Pancreatitis:* Pancreatitis was observed in 9 of the 2,613 adult patients (0.3%) who
 180 received EPIVIR in the controlled clinical trials EPV20001, NUCA3001, NUCB3001,
 181 NUCA3002, NUCB3002, and NUCB3007 [see *Warnings and Precautions (5.5)*].

182 *EPIVIR 300 mg Once Daily:* The types and frequencies of clinical adverse reactions
 183 reported in patients receiving EPIVIR 300 mg once daily or EPIVIR 150 mg twice daily (in
 184 3-drug combination regimens in EPV20001 and EPV40001) for 48 weeks were similar.

185 Selected laboratory abnormalities observed during therapy are summarized in Table 4.

186

187 **Table 4. Frequencies of Selected Grade 3-4 Laboratory Abnormalities in Adults in Four**
188 **24-Week Surrogate Endpoint Studies (NUCA3001, NUCA3002, NUCB3001, NUCB3002)**
189 **and a Clinical Endpoint Study (NUCB3007)**

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%

190 * The median duration on study was 12 months.

191 † Either zidovudine monotherapy or zidovudine in combination with zalcitabine.

192 ‡ Current therapy was either zidovudine, zidovudine plus didanosine, or zidovudine plus
193 zalcitabine.

194 ULN = Upper limit of normal.

195 ND = Not done.

196

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

200 Pediatric Patients – Clinical Trials in HIV-1: EPIVIR Oral Solution has been studied
201 in 638 pediatric patients 3 months to 18 years of age in 3 clinical trials.

202 Selected clinical adverse reactions and physical findings with a $\geq 5\%$ frequency during
203 therapy with EPIVIR 4 mg/kg twice daily plus RETROVIR 160 mg/m² 3 times daily in
204 therapy-naive (≤ 56 days of antiretroviral therapy) pediatric patients are listed in Table 5.

205

206 **Table 5. Selected Clinical Adverse Reactions and Physical Findings (≥5% Frequency) in**
 207 **Pediatric Patients in Study ACTG300**

Adverse Reaction	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%

208 *Includes pain, discharge, erythema, or swelling of an ear.
 209

210 *Pancreatitis:* Pancreatitis, which has been fatal in some cases, has been observed in
 211 antiretroviral nucleoside-experienced pediatric patients receiving EPIVIR alone or in
 212 combination with other antiretroviral agents. In an open-label dose-escalation study
 213 (NUCA2002), 14 patients (14%) developed pancreatitis while receiving monotherapy with
 214 EPIVIR. Three of these patients died of complications of pancreatitis. In a second open-label
 215 study (NUCA2005), 12 patients (18%) developed pancreatitis. In Study ACTG300, pancreatitis
 216 was not observed in 236 patients randomized to EPIVIR plus RETROVIR. Pancreatitis was
 217 observed in 1 patient in this study who received open-label EPIVIR in combination with
 218 RETROVIR and ritonavir following discontinuation of didanosine monotherapy [see *Warnings*
 219 *and Precautions (5.5)*].

220 *Paresthesias and Peripheral Neuropathies:* Paresthesias and peripheral
 221 neuropathies were reported in 15 patients (15%) in Study NUCA2002, 6 patients (9%) in Study
 222 NUCA2005, and 2 patients (<1%) in Study ACTG300.

223 Selected laboratory abnormalities experienced by therapy-naïve (≤56 days of
 224 antiretroviral therapy) pediatric patients are listed in Table 6.
 225

226 **Table 6. Frequencies of Selected Grade 3-4 Laboratory Abnormalities in Pediatric Patients**
 227 **in Study 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%

228 ULN = Upper limit of normal.

229
 230 **Neonates - Clinical Trials in HIV-1:** Limited short-term safety information is available
 231 from 2 small, uncontrolled studies in South Africa in neonates receiving lamivudine with or
 232 without zidovudine for the first week of life following maternal treatment starting at Week 38 or
 233 36 of gestation [see *Clinical Pharmacology (12.3)*]. Selected adverse reactions reported in these
 234 neonates included increased liver function tests, anemia, diarrhea, electrolyte disturbances,
 235 hypoglycemia, jaundice and hepatomegaly, rash, respiratory infections, and sepsis; 3 neonates
 236 died (1 from gastroenteritis with acidosis and convulsions, 1 from traumatic injury, and 1 from
 237 unknown causes). Two other nonfatal gastroenteritis or diarrhea cases were reported, including
 238 1 with convulsions; 1 infant had transient renal insufficiency associated with dehydration. The
 239 absence of control groups limits assessments of causality, but it should be assumed that
 240 perinatally exposed infants may be at risk for adverse reactions comparable to those reported in
 241 pediatric and adult HIV-1-infected patients treated with lamivudine-containing combination
 242 regimens. Long-term effects of in utero and infant lamivudine exposure are not known.

243 **6.2 Postmarketing Experience**

244 In addition to adverse reactions reported from clinical trials, the following adverse
 245 reactions have been reported during postmarketing use of EPIVIR. Because these reactions are
 246 reported voluntarily from a population of unknown size, estimates of frequency cannot be made.
 247 These reactions have been chosen for inclusion due to a combination of their seriousness,
 248 frequency of reporting, or potential causal connection to lamivudine.

249 **Body as a Whole:** Redistribution/accumulation of body fat [see *Warnings and*
 250 *Precautions (5.7)*].

251 **Endocrine and Metabolic:** Hyperglycemia.

252 **General:** Weakness.

253 **Hemic and Lymphatic:** Anemia (including pure red cell aplasia and severe anemias
 254 progressing on therapy).

255 **Hepatic and Pancreatic:** Lactic acidosis and hepatic steatosis, posttreatment
 256 exacerbation of hepatitis B [see *Boxed Warning, Warnings and Precautions (5.1, 5.2)*].

257 Hypersensitivity: Anaphylaxis, urticaria.
258 Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.
259 Skin: Alopecia, pruritus.

260 **7 DRUG INTERACTIONS**

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

266 **7.1 Interferon- and Ribavirin-Based Regimens**

267 Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of
268 HIV-1/HCV virologic suppression) was seen when ribavirin was coadministered with
269 lamivudine in HIV-1/HCV co-infected patients, hepatic decompensation (some fatal) has
270 occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for
271 HIV-1 and interferon alfa with or without ribavirin [*see Warnings and Precautions (5.4),*
272 *Clinical Pharmacology (12.3)*].

273 **7.2 Zalcitabine**

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

276 **7.3 Trimethoprim/Sulfamethoxazole (TMP/SMX)**

277 No change in dose of either drug is recommended. There is no information regarding the
278 effect on lamivudine pharmacokinetics of higher doses of TMP/SMX such as those used to treat
279 PCP.

280 **7.4 Drugs with No Observed Interactions With EPIVIR**

281 A drug interaction study showed no clinically significant interaction between EPIVIR
282 and zidovudine.

283 **8 USE IN SPECIFIC POPULATIONS**

284 **8.1 Pregnancy**

285 Pregnancy Category C. There are no adequate and well-controlled studies of EPIVIR in
286 pregnant women. Animal reproduction studies in rats and rabbits revealed no evidence of
287 teratogenicity. Increased early embryoletality occurred in rabbits at exposure levels similar to
288 those in humans. EPIVIR should be used during pregnancy only if the potential benefit justifies
289 the potential risk to the fetus.

290 Lamivudine pharmacokinetics were studied in pregnant women during 2 clinical studies
291 conducted in South Africa. The study assessed pharmacokinetics in: 16 women at 36 weeks
292 gestation using 150 mg lamivudine twice daily with zidovudine, 10 women at 38 weeks gestation
293 using 150 mg lamivudine twice daily with zidovudine, and 10 women at 38 weeks gestation
294 using lamivudine 300 mg twice daily without other antiretrovirals. These studies were not
295 designed or powered to provide efficacy information. Lamivudine pharmacokinetics in the

296 pregnant women were similar to those seen in non-pregnant adults and in postpartum women.
297 Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord
298 serum samples. In a subset of subjects, lamivudine amniotic fluid specimens were collected
299 following natural rupture of membranes. Amniotic fluid concentrations of lamivudine were
300 typically 2 times greater than maternal serum levels and ranged from 1.2 to 2.5 mcg/mL (150 mg
301 twice daily) and 2.1 to 5.2 mcg/mL (300 mg twice daily). It is not known whether risks of
302 adverse events associated with lamivudine are altered in pregnant women compared with other
303 HIV-1-infected patients.

304 Animal reproduction studies performed at oral doses up to 130 and 60 times the adult
305 dose in rats and rabbits, respectively, revealed no evidence of teratogenicity due to lamivudine.
306 Increased early embryolethality occurred in rabbits at exposure levels similar to those in humans.
307 However, there was no indication of this effect in rats at exposure levels up to 35 times those in
308 humans. Based on animal studies, lamivudine crosses the placenta and is transferred to the fetus.
309 [see *Nonclinical Toxicology (13.2)*].

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

313 **8.3 Nursing Mothers**

314 The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers
315 in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1
316 infection. Because of the potential for serious adverse reactions in nursing infants and HIV-1
317 transmission, mothers should be instructed not to breastfeed if they are receiving lamivudine.

318 Lamivudine is excreted into human milk. Samples of breast milk obtained from
319 20 mothers receiving lamivudine monotherapy (300 mg twice daily) or combination therapy
320 (150 mg lamivudine twice daily and 300 mg zidovudine twice daily) had measurable
321 concentrations of lamivudine.

322 **8.4 Pediatric Use**

323 The safety and effectiveness of twice-daily EPIVIR in combination with other
324 antiretroviral agents have been established in pediatric patients 3 months of age and older [see
325 *Adverse Reactions (6.1)*, *Clinical Pharmacology (12.3)*, *Clinical Studies (14.2)*].

326 **8.5 Geriatric Use**

327 Clinical studies of EPIVIR did not include sufficient numbers of subjects aged 65 and
328 over to determine whether they respond differently from younger subjects. In general, dose
329 selection for an elderly patient should be cautious, reflecting the greater frequency of decreased
330 hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. In
331 particular, because lamivudine is substantially excreted by the kidney and elderly patients are
332 more likely to have decreased renal function, renal function should be monitored and dosage
333 adjustments should be made accordingly [see *Dosage and Administration (2.3)*, *Clinical
334 Pharmacology (12.3)*].

335 **8.6 Patients With Impaired Renal Function**

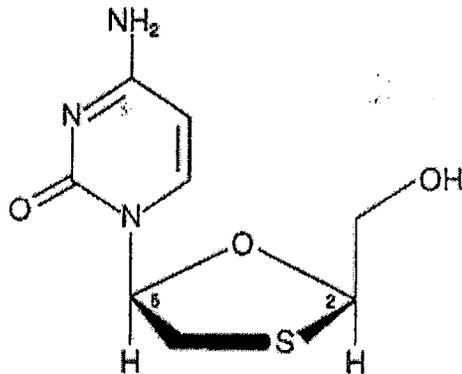
336 Reduction of the dosage of EPIVIR is recommended for patients with impaired renal
337 function [see Dosage and Administration (2.3), Clinical Pharmacology (12.3)].

338 10 OVERDOSAGE

339 There is no known antidote for EPIVIR. One case of an adult ingesting 6 g of EPIVIR
340 was reported; there were no clinical signs or symptoms noted and hematologic tests remained
341 normal. Two cases of pediatric overdose were reported in ACTG300. One case involved a single
342 dose of 7 mg/kg of EPIVIR; the second case involved use of 5 mg/kg of EPIVIR twice daily for
343 30 days. There were no clinical signs or symptoms noted in either case. Because a negligible
344 amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal
345 dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would
346 provide clinical benefit in a lamivudine overdose event. If overdose occurs, the patient should be
347 monitored, and standard supportive treatment applied as required.

348 11 DESCRIPTION

349 EPIVIR (also known as 3TC) is a brand name for lamivudine, a synthetic nucleoside
350 analogue with activity against HIV-1 and HBV. The chemical name of lamivudine is (2R,cis)-4-
351 amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the
352 (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)-2',3'-
353 dideoxy, 3'-thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of
354 229.3. It has the following structural formula:



355 Lamivudine is a white to off-white crystalline solid with a solubility of approximately
356 70 mg/mL in water at 20°C.

357
358 EPIVIR Tablets are for oral administration. Each scored 150-mg film-coated tablet
359 contains 150 mg of lamivudine and the inactive ingredients hypromellose, magnesium stearate,
360 microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, and
361 titanium dioxide.

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

365 EPIVIR Oral Solution is for oral administration. One milliliter (1 mL) of EPIVIR Oral

366 Solution contains 10 mg of lamivudine (10 mg/mL) in an aqueous solution and the inactive
367 ingredients artificial strawberry and banana flavors, citric acid (anhydrous), methylparaben,
368 propylene glycol, propylparaben, sodium citrate (dihydrate), and sucrose (200 mg).

369 **12 CLINICAL PHARMACOLOGY**

370 **12.1 Mechanism of Action**

371 Lamivudine is an antiviral agent [see *Clinical Pharmacology* (12.4)].

372 **12.3 Pharmacokinetics**

373 Pharmacokinetics in Adults: The pharmacokinetic properties of lamivudine have been
374 studied in asymptomatic, HIV-1-infected adult patients after administration of single intravenous
375 (IV) doses ranging from 0.25 to 8 mg/kg, as well as single and multiple (twice-daily regimen)
376 oral doses ranging from 0.25 to 10 mg/kg.

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

379 The steady-state pharmacokinetic properties of the EPIVIR 300-mg tablet once daily for
380 7 days compared with the EPIVIR 150-mg tablet twice daily for 7 days were assessed in a
381 crossover study in 60 healthy volunteers. EPIVIR 300 mg once daily resulted in lamivudine
382 exposures that were similar to EPIVIR 150 mg twice daily with respect to plasma $AUC_{24,ss}$;
383 however, $C_{max,ss}$ was 66% higher and the trough value was 53% lower compared with the
384 150-mg twice-daily regimen. Intracellular lamivudine triphosphate exposures in peripheral blood
385 mononuclear cells were also similar with respect to $AUC_{24,ss}$ and $C_{max24,ss}$; however, trough
386 values were lower compared with the 150-mg twice-daily regimen. Inter-subject variability was
387 greater for intracellular lamivudine triphosphate concentrations versus lamivudine plasma trough
388 concentrations. The clinical significance of observed differences for both plasma lamivudine
389 concentrations and intracellular lamivudine triphosphate concentrations is not known.

390 Absorption and Bioavailability: Lamivudine was rapidly absorbed after oral
391 administration in HIV-1-infected patients. Absolute bioavailability in 12 adult patients was
392 $86\% \pm 16\%$ (mean \pm SD) for the 150-mg tablet and $87\% \pm 13\%$ for the oral solution. After oral
393 administration of 2 mg/kg twice a day to 9 adults with HIV-1, the peak serum lamivudine
394 concentration (C_{max}) was 1.5 ± 0.5 mcg/mL (mean \pm SD). The area under the plasma
395 concentration versus time curve (AUC) and C_{max} increased in proportion to oral dose over the
396 range from 0.25 to 10 mg/kg.

397 The accumulation ratio of lamivudine in HIV-1-positive asymptomatic adults with
398 normal renal function was 1.50 following 15 days of oral administration of 2 mg/kg twice daily.

399 Effects of Food on Oral Absorption: An investigational 25-mg dosage form of
400 lamivudine was administered orally to 12 asymptomatic, HIV-1-infected patients on 2 occasions,
401 once in the fasted state and once with food (1,099 kcal; 75 grams fat, 34 grams protein, 72 grams
402 carbohydrate). Absorption of lamivudine was slower in the fed state (T_{max} : 3.2 ± 1.3 hours)
403 compared with the fasted state (T_{max} : 0.9 ± 0.3 hours); C_{max} in the fed state was $40\% \pm 23\%$
404 (mean \pm SD) lower than in the fasted state. There was no significant difference in systemic

405 exposure (AUC_{∞}) in the fed and fasted states; therefore, EPIVIR Tablets and Oral Solution may
 406 be administered with or without food.

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

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

414 **Metabolism:** Metabolism of lamivudine is a minor route of elimination. In man, the
 415 only known metabolite of lamivudine is the trans-sulfoxide metabolite. Within 12 hours after a
 416 single oral dose of lamivudine in 6 HIV-1-infected adults, $5.2\% \pm 1.4\%$ (mean \pm SD) of the dose
 417 was excreted as the trans-sulfoxide metabolite in the urine. Serum concentrations of this
 418 metabolite have not been determined.

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

424 In most single-dose studies in HIV-1-infected patients, HBV-infected patients, or healthy
 425 subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life
 426 ($t_{1/2}$) ranged from 5 to 7 hours. In HIV-1-infected patients, total clearance was
 427 398.5 ± 69.1 mL/min (mean \pm SD). Oral clearance and elimination half-life were independent of
 428 dose and body weight over an oral dosing range from 0.25 to 10 mg/kg.

429 **Special Populations: Renal Impairment:** The pharmacokinetic properties of
 430 lamivudine have been determined in a small group of HIV-1-infected adults with impaired renal
 431 function (Table 7).
 432

433 **Table 7. Pharmacokinetic Parameters (Mean \pm SD) After a Single 300-mg Oral Dose of**
 434 **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

435
 436 Exposure (AUC_{∞}), C_{max} , and half-life increased with diminishing renal function (as

437 expressed by creatinine clearance). Apparent total oral clearance (Cl/F) of lamivudine decreased
438 as creatinine clearance decreased. T_{max} was not significantly affected by renal function. Based on
439 these observations, it is recommended that the dosage of lamivudine be modified in patients with
440 renal impairment [see *Dosage and Administration (2.3)*].

441 Based on a study in otherwise healthy subjects with impaired renal function,
442 hemodialysis increased lamivudine clearance from a mean of 64 to 88 mL/min; however, the
443 length of time of hemodialysis (4 hours) was insufficient to significantly alter mean lamivudine
444 exposure after a single-dose administration. Continuous ambulatory peritoneal dialysis and
445 automated peritoneal dialysis have negligible effects on lamivudine clearance. Therefore, it is
446 recommended, following correction of dose for creatinine clearance, that no additional dose
447 modification be made after routine hemodialysis or peritoneal dialysis.

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

450 The effects of renal impairment on lamivudine pharmacokinetics in pediatric patients are
451 not known.

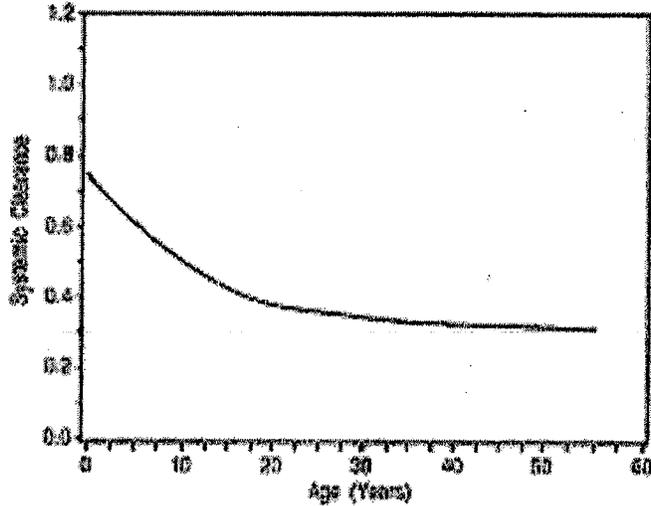
452 **Hepatic Impairment:** The pharmacokinetic properties of lamivudine have been
453 determined in adults with impaired hepatic function. Pharmacokinetic parameters were not
454 altered by diminishing hepatic function; therefore, no dose adjustment for lamivudine is required
455 for patients with impaired hepatic function. Safety and efficacy of lamivudine have not been
456 established in the presence of decompensated liver disease.

457 **Pediatric Patients:** In Study NUCA2002, pharmacokinetic properties of lamivudine
458 were assessed in a subset of 57 HIV-1-infected pediatric patients (age range: 4.8 months to
459 16 years, weight range: 5 to 66 kg) after oral and IV administration of 1, 2, 4, 8, 12, and
460 20 mg/kg/day. In the 9 infants and children (range: 5 months to 12 years of age) receiving oral
461 solution 4 mg/kg twice daily (the usual recommended pediatric dose), absolute bioavailability
462 was $66\% \pm 26\%$ (mean \pm SD), which was less than the $86\% \pm 16\%$ (mean \pm SD) observed in
463 adults. The mechanism for the diminished absolute bioavailability of lamivudine in infants and
464 children is unknown.

465 Systemic clearance decreased with increasing age in pediatric patients, as shown in
466 Figure 1.

467

468 **Figure 1. Systemic Clearance (L/hr•kg) of Lamivudine in Relation to Age**



469
470

471 After oral administration of lamivudine 4 mg/kg twice daily to 11 pediatric patients
472 ranging from 4 months to 14 years of age, C_{max} was 1.1 ± 0.6 mcg/mL and half-life was
473 2.0 ± 0.6 hours. (In adults with similar blood sampling, the half-life was 3.7 ± 1 hours.) Total
474 exposure to lamivudine, as reflected by mean AUC values, was comparable between pediatric
475 patients receiving an 8-mg/kg/day dose and adults receiving a 4-mg/kg/day dose.

476 Distribution of lamivudine into cerebrospinal fluid (CSF) was assessed in 38 pediatric
477 patients after multiple oral dosing with lamivudine. CSF samples were collected between 2 and
478 4 hours postdose. At the dose of 8 mg/kg/day, CSF lamivudine concentrations in 8 patients
479 ranged from 5.6% to 30.9% (mean \pm SD of $14.2\% \pm 7.9\%$) of the concentration in a
480 simultaneous serum sample, with CSF lamivudine concentrations ranging from 0.04 to
481 0.3 mcg/mL.

482 Limited, uncontrolled pharmacokinetic and safety data are available from administration
483 of lamivudine (and zidovudine) to 36 infants up to 1 week of age in 2 studies in South Africa. In
484 these studies, lamivudine clearance was substantially reduced in 1-week-old neonates relative to
485 pediatric patients (>3 months of age) studied previously. There is insufficient information to
486 establish the time course of changes in clearance between the immediate neonatal period and the
487 age-ranges >3 months old [see *Adverse Reactions* (6.1)].

488 **Geriatric Patients:** The pharmacokinetics of lamivudine after administration of
489 EPIVIR to patients over 65 years of age have not been studied [see *Use in Specific Populations*
490 (8.5)].

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

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

493 **Drug Interactions: Interferon Alfa:** There was no significant pharmacokinetic
494 interaction between lamivudine and interferon alfa in a study of 19 healthy male subjects [see
495 *Warnings and Precautions* (5.4)].

496 *Ribavirin*: In vitro data indicate ribavirin reduces phosphorylation of lamivudine,
497 stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or
498 intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss
499 of HIV-1/HCV virologic suppression) interaction was observed when ribavirin and lamivudine
500 (n = 18), stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug
501 regimen to HIV-1/HCV co-infected patients [see *Warnings and Precautions* (5.4)].

502 *Trimethoprim/Sulfamethoxazole*: Lamivudine and TMP/SMX were coadministered
503 to 14 HIV-1-positive patients in a single-center, open-label, randomized, crossover study. Each
504 patient received treatment with a single 300-mg dose of lamivudine and TMP 160 mg/SMX
505 800 mg once a day for 5 days with concomitant administration of lamivudine 300 mg with the
506 fifth dose in a crossover design. Coadministration of TMP/SMX with lamivudine resulted in an
507 increase of $43\% \pm 23\%$ (mean \pm SD) in lamivudine AUC $_{\infty}$, a decrease of $29\% \pm 13\%$ in
508 lamivudine oral clearance, and a decrease of $30\% \pm 36\%$ in lamivudine renal clearance. The
509 pharmacokinetic properties of TMP and SMX were not altered by coadministration with
510 lamivudine [see *Drug Interactions* (7.3)].

511 *Zidovudine*: No clinically significant alterations in lamivudine or zidovudine
512 pharmacokinetics were observed in 12 asymptomatic HIV-1-infected adult patients given a
513 single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg q
514 12 hr) [see *Drug Interactions* (7.4)].

515 **12.4 Microbiology**

516 Mechanism of Action: Intracellularly, lamivudine is phosphorylated to its active
517 5'-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of
518 3TC-TP is the inhibition of HIV-1 reverse transcriptase (RT) via DNA chain termination after
519 incorporation of the nucleotide analogue into viral DNA. 3TC-TP is a weak inhibitor of
520 mammalian DNA polymerases α , β , and γ .

521 Antiviral Activity: The antiviral activity of lamivudine against HIV-1 was assessed in a
522 number of cell lines (including monocytes and fresh human peripheral blood lymphocytes) using
523 standard susceptibility assays. EC₅₀ values (50% effective concentrations) were in the range of
524 0.003 to 15 μ M (1 μ M = 0.23 mcg/mL). HIV-1 from therapy-naïve subjects with no amino acid
525 substitutions associated with resistance gave median EC₅₀ values of 0.429 μ M (range: 0.200 to
526 2.007 μ M) from Virco (n = 92 baseline samples from COLA40263) and 2.35 μ M (1.37 to
527 3.68 μ M) from Monogram Biosciences (n = 135 baseline samples from ESS30009). The EC₅₀
528 values of lamivudine against different HIV-1 clades (A-G) ranged from 0.001 to 0.120 μ M, and
529 against HIV-2 isolates from 0.003 to 0.120 μ M in peripheral blood mononuclear cells. Ribavirin
530 (50 μ M) decreased the anti-HIV-1 activity of lamivudine by 3.5 fold in MT-4 cells. In HIV-
531 1-infected MT-4 cells, lamivudine in combination with zidovudine at various ratios exhibited
532 synergistic antiretroviral activity. Please see the full prescribing information for EPIVIR-HBV
533 for information regarding the inhibitory activity of lamivudine against HBV.

534 Resistance: Lamivudine-resistant variants of HIV-1 have been selected in cell culture.
535 Genotypic analysis showed that the resistance was due to a specific amino acid substitution in

536 the HIV-1 reverse transcriptase at codon 184 changing the methionine to either isoleucine or
537 valine (M184V/I).

538 HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from
539 patients. Susceptibility of clinical isolates to lamivudine and zidovudine was monitored in
540 controlled clinical trials. In patients receiving lamivudine monotherapy or combination therapy
541 with lamivudine plus zidovudine, HIV-1 isolates from most patients became phenotypically and
542 genotypically resistant to lamivudine within 12 weeks. In some patients harboring
543 zidovudine-resistant virus at baseline, phenotypic sensitivity to zidovudine was restored by
544 12 weeks of treatment with lamivudine and zidovudine. Combination therapy with lamivudine
545 plus zidovudine delayed the emergence of mutations conferring resistance to zidovudine.

546 Lamivudine-resistant HBV isolates develop substitutions (rtM204V/I) in the YMDD
547 motif of the catalytic domain of the viral reverse transcriptase. rtM204V/I substitutions are
548 frequently accompanied by other substitutions (rtV173L, rtL180M) which enhance the level of
549 lamivudine resistance or act as compensatory mutations improving replication efficiency. Other
550 substitutions detected in lamivudine-resistant HBV isolates include: rtL80I and rtA181T. Similar
551 HBV mutants have been reported in HIV-1-infected patients who received
552 lamivudine-containing antiretroviral regimens in the presence of concurrent infection with
553 hepatitis B virus [see *Warnings and Precautions* (5.2)].

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

558 Genotypic and Phenotypic Analysis of On-Therapy HIV-1 Isolates From Patients
559 With Virologic Failure: Study EPV20001: Fifty-three of 554 (10%) patients enrolled in
560 EPV20001 were identified as virological failures (plasma HIV-1 RNA level ≥ 400 copies/mL) by
561 Week 48. Twenty-eight patients were randomized to the lamivudine once-daily treatment group
562 and 25 to the lamivudine twice-daily treatment group. The median baseline plasma HIV-1 RNA
563 levels of patients in the lamivudine once-daily group and lamivudine twice-daily group were
564 4.9 log₁₀ copies/mL and 4.6 log₁₀ copies/mL, respectively.

565 Genotypic analysis of on-therapy isolates from 22 patients identified as virologic failures
566 in the lamivudine once-daily group showed that isolates from 0/22 patients contained
567 treatment-emergent amino acid substitutions associated with zidovudine resistance (M41L,
568 D67N, K70R, L210W, T215Y/F, or K219Q/E), isolates from 10/22 patients contained
569 treatment-emergent amino acid substitutions associated with efavirenz resistance (L100I, K101E,
570 K103N, V108I, or Y181C), and isolates from 8/22 patients contained a treatment-emergent
571 lamivudine resistance-associated substitution (M184I or M184V).

572 Genotypic analysis of on-therapy isolates from patients (n = 22) in the lamivudine
573 twice-daily treatment group showed that isolates from 1/22 patients contained
574 treatment-emergent zidovudine resistance substitutions, isolates from 7/22 contained
575 treatment-emergent efavirenz resistance substitutions, and isolates from 5/22 contained

576 treatment-emergent lamivudine resistance substitutions.

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

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

587 *Study EPV40001*: Fifty patients received zidovudine 300 mg twice daily plus
588 abacavir 300 mg twice daily plus lamivudine 300 mg once daily and 50 patients received
589 zidovudine 300 mg plus abacavir 300 mg plus lamivudine 150 mg all twice daily. The median
590 baseline plasma HIV-1 RNA levels for patients in the 2 groups were 4.79 log₁₀ copies/mL and
591 4.83 log₁₀ copies/mL, respectively. Fourteen of 50 patients in the lamivudine once-daily
592 treatment group and 9 of 50 patients in the lamivudine twice-daily group were identified as
593 virologic failures.

594 Genotypic analysis of on-therapy HIV-1 isolates from patients (n = 9) in the lamivudine
595 once-daily treatment group showed that isolates from 6 patients had an abacavir and/or
596 lamivudine resistance-associated substitution M184V alone. On-therapy isolates from patients
597 (n = 6) receiving lamivudine twice daily showed that isolates from 2 patients had M184V alone,
598 and isolates from 2 patients harbored the M184V substitution in combination with zidovudine
599 resistance-associated amino acid substitutions.

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

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

606 **13 NONCLINICAL TOXICOLOGY**

607 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

608 Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence
609 of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) those observed in
610 humans at the recommended therapeutic dose for HIV-1 infection. Lamivudine was not active in
611 a microbial mutagenicity screen or an in vitro cell transformation assay, but showed weak
612 in vitro mutagenic activity in a cytogenetic assay using cultured human lymphocytes and in the
613 mouse lymphoma assay. However, lamivudine showed no evidence of in vivo genotoxic activity
614 in the rat at oral doses of up to 2,000 mg/kg, producing plasma levels of 35 to 45 times those in

615 humans at the recommended dose for HIV-1 infection. In a study of reproductive performance,
 616 lamivudine administered to rats at doses up to 4,000 mg/kg/day, producing plasma levels 47 to
 617 70 times those in humans, revealed no evidence of impaired fertility and no effect on the
 618 survival, growth, and development to weaning of the offspring.

619 **13.2 Reproductive Toxicology Studies**

620 Reproduction studies have been performed in rats and rabbits at orally administered doses
 621 up to 4,000 mg/kg/day and 1,000 mg/kg/day, respectively, producing plasma levels up to
 622 approximately 35 times that for the adult HIV dose. No evidence of teratogenicity due to
 623 lamivudine was observed. Evidence of early embryoletality was seen in the rabbit at exposure
 624 levels similar to those observed in humans, but there was no indication of this effect in the rat at
 625 exposure levels up to 35 times those in humans. Studies in pregnant rats and rabbits showed that
 626 lamivudine is transferred to the fetus through the placenta.

627 **14 CLINICAL STUDIES**

628 The use of EPIVIR is based on the results of clinical studies in HIV-1-infected patients in
 629 combination regimens with other antiretroviral agents. Information from trials with clinical
 630 endpoints or a combination of CD4+ cell counts and HIV-1 RNA measurements is included
 631 below as documentation of the contribution of lamivudine to a combination regimen in
 632 controlled trials.

633 **14.1 Adults**

634 Clinical Endpoint Study: NUCB3007 (CAESAR) was a multi-center, double-blind,
 635 placebo-controlled study comparing continued current therapy (zidovudine alone [62% of
 636 patients] or zidovudine with didanosine or zalcitabine [38% of patients]) to the addition of
 637 EPIVIR or EPIVIR plus an investigational non-nucleoside reverse transcriptase inhibitor
 638 (NNRTI), randomized 1:2:1. A total of 1,816 HIV-1-infected adults with 25 to
 639 250 CD4+ cells/mm³ (median = 122 cells/mm³) at baseline were enrolled: median age was
 640 36 years, 87% were male, 84% were nucleoside-experienced, and 16% were therapy-naive. The
 641 median duration on study was 12 months. Results are summarized in Table 8.
 642

643 **Table 8. Number of Patients (%) With at Least One HIV-1 Disease Progression Event or**
 644 **Death**

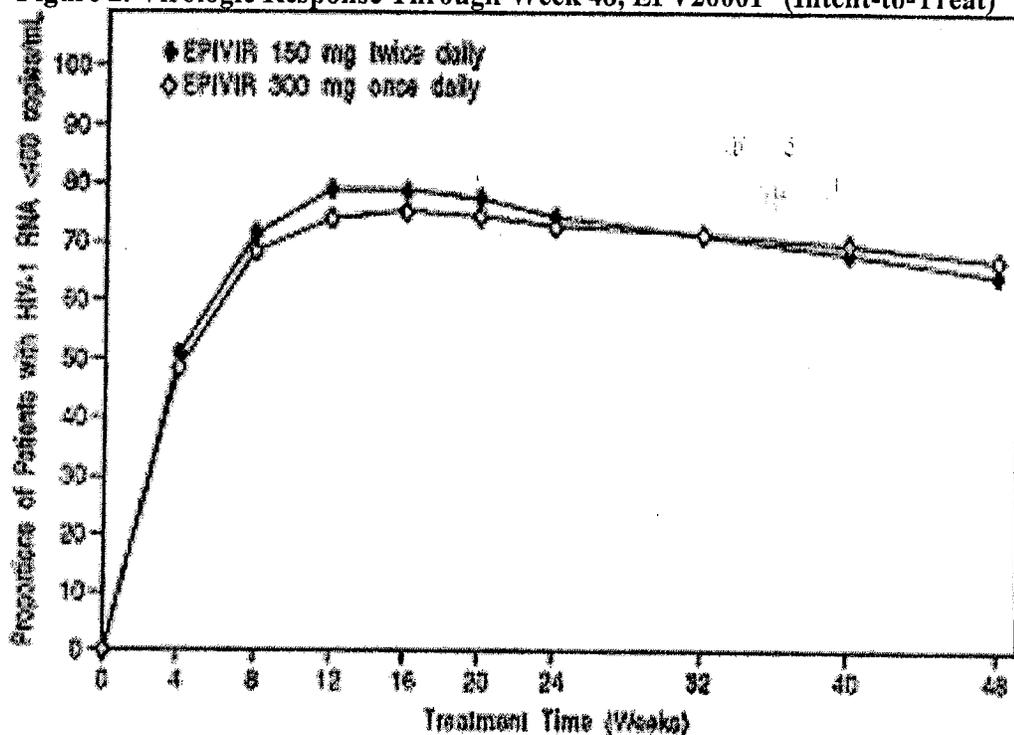
Endpoint	Current Therapy (n = 460)	EPIVIR plus Current Therapy (n = 896)	EPIVIR plus an NNRTI* plus Current Therapy (n = 460)
HIV-1 progression or death	90 (19.6%)	86 (9.6%)	41 (8.9%)
Death	27 (5.9%)	23 (2.6%)	14 (3.0%)

645 * An investigational non-nucleoside reverse transcriptase inhibitor not approved in the United
 646 States.
 647

648 Surrogate Endpoint Studies: Dual Nucleoside Analogue Studies: Principal clinical
649 trials in the initial development of lamivudine compared lamivudine/zidovudine combinations
650 with zidovudine monotherapy or with zidovudine plus zalcitabine. These studies demonstrated
651 the antiviral effect of lamivudine in a 2-drug combination. More recent uses of lamivudine in
652 treatment of HIV-1 infection incorporate it into multiple-drug regimens containing at least
653 3 antiretroviral drugs for enhanced viral suppression.

654 Dose Regimen Comparison Surrogate Endpoint Studies in Therapy-Naive
655 Adults: EPV20001 was a multi-center, double-blind, controlled study in which patients were
656 randomized 1:1 to receive EPIVIR 300 mg once daily or EPIVIR 150 mg twice daily, in
657 combination with zidovudine 300 mg twice daily and efavirenz 600 mg once daily. A total of
658 554 antiretroviral treatment-naive HIV-1-infected adults enrolled: male (79%), Caucasian (50%),
659 median age of 35 years, baseline CD4+ cell counts of 69 to 1,089 cells/mm³
660 (median = 362 cells/mm³), and median baseline plasma HIV-1 RNA of 4.66 log₁₀ copies/mL.
661 Outcomes of treatment through 48 weeks are summarized in Figure 2 and Table 9.
662

663 **Figure 2. Virologic Response Through Week 48, EPV20001^{††}(Intent-to-Treat)**



664
665
666 * Roche AMPLICOR HIV-1 MONITOR.
667 † Responders at each visit are patients who had achieved and maintained HIV-1 RNA
668 <400 copies/mL without discontinuation by that visit.
669

670 **Table 9. Outcomes of Randomized Treatment Through 48 Weeks (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%

671 * Achieved confirmed plasma HIV-1 RNA <400 copies/mL and maintained through 48 weeks.
 672 † Achieved suppression but rebounded by Week 48, discontinued due to virologic failure,
 673 insufficient viral response according to the investigator, or never suppressed through Week 48.
 674 ‡ Includes consent withdrawn, lost to followup, protocol violation, data outside the study-defined
 675 schedule, and randomized but never initiated treatment.

676
 677 The proportions of patients with HIV-1 RNA <50 copies/mL (via Roche Ultrasensitive
 678 assay) through Week 48 were 61% for patients receiving EPIVIR 300 mg once daily and 63%
 679 for patients receiving EPIVIR 150 mg twice daily. Median increases in CD4+ cell counts were
 680 144 cells/mm³ at Week 48 in patients receiving EPIVIR 300 mg once daily and 146 cells/mm³ for
 681 patients receiving EPIVIR 150 mg twice daily.

682 A small, randomized, open-label pilot study, EPV40001, was conducted in Thailand. A
 683 total of 159 treatment-naïve adult patients (male 32%, Asian 100%, median age 30 years,
 684 baseline median CD4+ cell count 380 cells/mm³, median plasma HIV-1 RNA
 685 4.8 log₁₀ copies/mL) were enrolled. Two of the treatment arms in this study provided a
 686 comparison between lamivudine 300 mg once daily (n = 54) and lamivudine 150 mg twice daily
 687 (n = 52), each in combination with zidovudine 300 mg twice daily and abacavir 300 mg twice
 688 daily. In intent-to-treat analyses of 48-week data, the proportions of patients with HIV-1 RNA
 689 below 400 copies/mL were 61% (33/54) in the group randomized to once-daily lamivudine and
 690 75% (39/52) in the group randomized to receive all 3 drugs twice daily; the proportions with
 691 HIV-1 RNA below 50 copies/mL were 54% (29/54) in the once-daily lamivudine group and 67%
 692 (35/52) in the all-twice-daily group; and the median increases in CD4+ cell counts were
 693 166 cells/mm³ in the once-daily lamivudine group and 216 cells/mm³ in the all-twice-daily
 694 group.

695 **14.2 Pediatric Patients**

696 Clinical Endpoint Study: ACTG300 was a multi-center, randomized, double-blind study
 697 that provided for comparison of EPIVIR plus RETROVIR (zidovudine) with didanosine
 698 monotherapy. A total of 471 symptomatic, HIV-1-infected therapy-naïve (≤56 days of
 699 antiretroviral therapy) pediatric patients were enrolled in these 2 treatment arms. The median age

700 was 2.7 years (range: 6 weeks to 14 years), 58% were female, and 86% were non-Caucasian. The
 701 mean baseline CD4+ cell count was 868 cells/mm³ (mean: 1,060 cells/mm³ and range: 0 to
 702 4,650 cells/mm³ for patients ≤5 years of age; mean: 419 cells/mm³ and range: 0 to
 703 1,555 cells/mm³ for patients >5 years of age) and the mean baseline plasma HIV-1 RNA was
 704 5.0 log₁₀ copies/mL. The median duration on study was 10.1 months for the patients receiving
 705 EPIVIR plus RETROVIR and 9.2 months for patients receiving didanosine monotherapy.
 706 Results are summarized in Table 10.

707
 708 **Table 10. Number of Patients (%) Reaching a Primary Clinical Endpoint (Disease**
 709 **Progression or Death)**

Endpoint	EPIVIR plus RETROVIR (n = 236)	Didanosine (n = 235)
HIV-1 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%)

710

711 **16 HOW SUPPLIED/STORAGE AND HANDLING**

712 **EPIVIR Scored Tablets, 150 mg**

713 White, diamond-shaped, scored, film-coated tablets debossed with “GX CJ7” on both
 714 sides.

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

716 **EPIVIR Tablets, 300 mg**

717 Gray, modified diamond-shaped, film-coated tablets engraved with “GX EJ7” on one
 718 side and plain on the reverse side.

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

720 Recommended Storage:

721 Store EPIVIR Tablets at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F)
 722 [see USP Controlled Room Temperature].

723 **EPIVIR Oral Solution, 10 mg/mL**

724 A clear, colorless to pale yellow, strawberry-banana-flavored liquid, contains 10 mg of
 725 lamivudine in each 1 mL.

726 Plastic bottle of 240 mL (NDC 0173-0471-00) with child-resistant closure. This product
 727 does not require reconstitution.

728 Recommended Storage:

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

730 **17 PATIENT COUNSELING INFORMATION**

731 **17.1 Advice for the Patient**

732 Information About Therapy With EPIVIR: EPIVIR is not a cure for HIV-1 infection
733 and patients may continue to experience illnesses associated with HIV-1 infection, including
734 opportunistic infections. Patients should remain under the care of a physician when using
735 EPIVIR. Patients should be advised that the use of EPIVIR has not been shown to reduce the risk
736 of transmission of HIV-1 to others through sexual contact or blood contamination.

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

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

740 EPIVIR should not be coadministered with drugs containing lamivudine or emtricitabine,
741 including COMBIVIR (lamivudine/zidovudine) Tablets, EPZICOM (abacavir sulfate and
742 lamivudine) Tablets, TRIZIVIR (abacavir sulfate, lamivudine, and zidovudine), ATRIPLA
743 (efavirenz, emtricitabine, and tenofovir), EMTRIVA (emtricitabine) or TRUVADA
744 (emtricitabine and tenofovir) [see *Warnings and Precautions* (5.3)].

745 Redistribution/Accumulation of Body Fat: Patients should be informed that
746 redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy,
747 including EPIVIR, and that the cause and long-term health effects of these conditions are not
748 known at this time [see *Warnings and Precautions* (5.7)].

749 Differences in Formulations of EPIVIR: Patients should be advised that EPIVIR
750 Tablets and Oral Solution contain a higher dose of the same active ingredient (lamivudine) as
751 EPIVIR-HBV Tablets and Oral Solution. If a decision is made to include lamivudine in the
752 HIV-1 treatment regimen of a patient co-infected with HIV-1 and HBV, the formulation and
753 dosage of lamivudine in EPIVIR (not EPIVIR-HBV) should be used [see *Warnings and*
754 *Precautions* (5.2)].

755 Co-infection With HIV-1 and HBV: Patients co-infected with HIV-1 and HBV should
756 be informed that deterioration of liver disease has occurred in some cases when treatment with
757 lamivudine was discontinued. Patients should be advised to discuss any changes in regimen with
758 their physician [see *Warnings and Precautions* (5.2)].

759 Risk of Pancreatitis: Parents or guardians should be advised to monitor pediatric
760 patients for signs and symptoms of pancreatitis [see *Warnings and Precautions* (5.5)].

761 Sucrose Content of EPIVIR Oral Solution: Diabetic patients should be advised that
762 each 15-mL dose of EPIVIR Oral Solution contains 3 grams of sucrose [see *Description* (11)].

763
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