

## 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](http://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

## FULL PRESCRIBING INFORMATION: CONTENTS\*

WARNING: RISK OF LACTIC ACIDOSIS, EXACERBATIONS OF HEPATITIS B IN CO-INFECTED PATIENTS UPON DISCONTINUATION OF EPIVIR, DIFFERENT FORMULATIONS OF EPIVIR.

### 1 INDICATIONS AND USAGE

### 2 DOSAGE AND ADMINISTRATION

- 2.1 Adults and Adolescents >16 years of age
- 2.2 Pediatric Patients
- 2.3 Patients With Renal Impairment

### 3 DOSAGE FORMS AND STRENGTHS

### 4 CONTRAINDICATIONS

### 5 WARNINGS AND PRECAUTIONS

- 5.1 Lactic Acidosis/Severe Hepatomegaly With Steatosis
- 5.2 Patients With HIV-1 and Hepatitis B Virus Co-infection
- 5.3 Use With Other Lamivudine- and Emtricitabine-Containing Products
- 5.4 Use With Interferon- and Ribavirin-Based Regimens
- 5.5 Pancreatitis
- 5.6 Immune Reconstitution Syndrome
- 5.7 Fat Redistribution

### 6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

### 7 DRUG INTERACTIONS

- 7.1 Interferon- and Ribavirin-Based Regimens
- 7.2 Zalcitabine
- 7.3 Trimethoprim/Sulfamethoxazole (TMP/SMX)
- 7.4 Drugs with No Observed Interactions With EPIVIR

### 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Patients With Impaired Renal Function

### 10 OVERDOSAGE

### 11 DESCRIPTION

### 12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics
- 12.4 Microbiology

### 13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Reproductive Toxicology Studies

### 14 CLINICAL STUDIES

- 14.1 Adults
- 14.2 Pediatric Patients

### 16 HOW SUPPLIED/STORAGE AND HANDLING

### 17 PATIENT COUNSELING INFORMATION

- 17.1 Advice for the Patient

\*Sections or subsections omitted from the full prescribing information are not listed.

1

---

2 **FULL PRESCRIBING INFORMATION**

3 **WARNING: RISK OF LACTIC ACIDOSIS, EXACERBATIONS OF HEPATITIS B IN**  
4 **CO-INFECTED PATIENTS UPON DISCONTINUATION OF EPIVIR<sup>®</sup>, 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<sup>®</sup> 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  $\geq 14$  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) <sup>a</sup>	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-1<sup>2</sup> 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<sup>®</sup> (lamivudine/zidovudine) Tablets,  
105 EPZICOM<sup>®</sup> (abacavir sulfate and lamivudine) Tablets, or TRIZIVIR<sup>®</sup> (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<sup>™</sup> (efavirenz, emtricitabine, and tenofovir), EMTRIVA<sup>®</sup> (emtricitabine), or  
121 TRUVADA<sup>®</sup> (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<sup>®</sup> 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)
<b>Body as a Whole</b>		
Headache	35%	27%
Malaise & fatigue	27%	23%
Fever or chills	10%	12%
<b>Digestive</b>		
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%
<b>Nervous System</b>		
Neuropathy	12%	10%
Insomnia & other sleep disorders	11%	7%
Dizziness	10%	4%
Depressive disorders	9%	4%
<b>Respiratory</b>		
Nasal signs & symptoms	20%	11%
Cough	18%	13%
<b>Skin</b>		
Skin rashes	9%	6%
<b>Musculoskeletal</b>		
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/m<sup>2</sup> 3 times daily in  
204 therapy-naive ( $\leq 56$  days of antiretroviral therapy) pediatric patients are listed in Table 5.

205

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

Adverse Reaction	EPIVIR plus RETROVIR (n = 236)	Didanosine (n = 235)
<b>Body as a Whole</b>		
Fever	25%	32%
<b>Digestive</b>		
Hepatomegaly	11%	11%
Nausea & vomiting	8%	7%
Diarrhea	8%	6%
Stomatitis	6%	12%
Splenomegaly	5%	8%
<b>Respiratory</b>		
Cough	15%	18%
Abnormal breath sounds/wheezing	7%	9%
<b>Ear, Nose, and Throat</b>		
Signs or symptoms of ears*	7%	6%
Nasal discharge or congestion	8%	11%
<b>Other</b>		
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-naive ( $\leq 56$  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 <sup>3</sup> )	8%	3%
Hemoglobin (<7.0 g/dL)	4%	2%
Platelets (<50,000/mm <sup>3</sup> )	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**

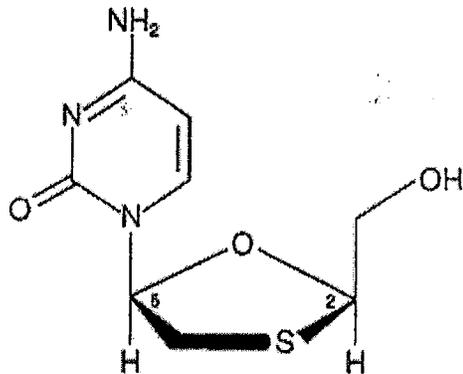
336 Reduction of the dosage of EPIVIR is recommended for patients with impaired renal  
337 function [see Dosage and Administration (2.3), Clinical Pharmacology (12.3)].

## 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.

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  $1.5 \pm 0.5$  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 ( $T_{max}$ :  $3.2 \pm 1.3$  hours)  
403 compared with the fasted state ( $T_{max}$ :  $0.9 \pm 0.3$  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 ( $AUC_{\infty}$ ) 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  $1.3 \pm 0.4$  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  $199.7 \pm 56.9$  mL/min (mean  $\pm$  SD). In 20 HIV-1-infected patients given a  
422 single IV dose, renal clearance was  $280.4 \pm 75.2$  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  $398.5 \pm 69.1$  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)	$111 \pm 14$	$28 \pm 8$	$6 \pm 2$
$C_{max}$ (mcg/mL)	$2.6 \pm 0.5$	$3.6 \pm 0.8$	$5.8 \pm 1.2$
$AUC_{\infty}$ (mcg·hr/mL)	$11.0 \pm 1.7$	$48.0 \pm 19$	$157 \pm 74$
Cl/F (mL/min)	$464 \pm 76$	$114 \pm 34$	$36 \pm 11$

435

436 Exposure ( $AUC_{\infty}$ ),  $C_{max}$ , 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.

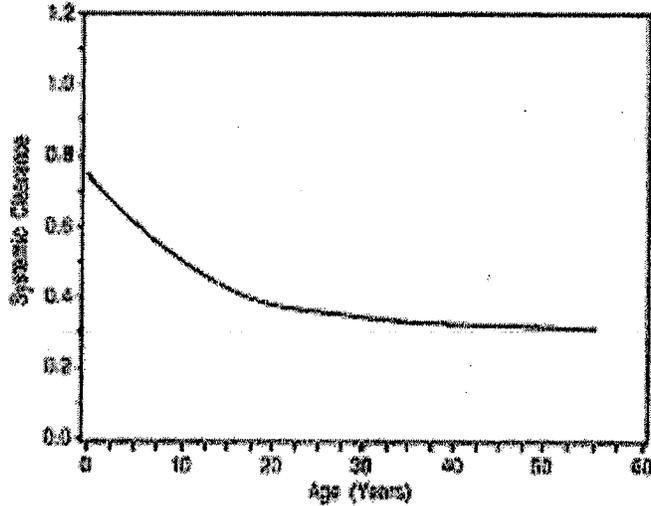
452 **Hepatic Impairment:** The pharmacokinetic properties of lamivudine have been  
453 determined in adults with impaired hepatic function. Pharmacokinetic parameters were not  
454 altered by diminishing hepatic function; therefore, no dose adjustment for lamivudine is required  
455 for patients 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  $1.1 \pm 0.6$  mcg/mL and half-life was  
473  $2.0 \pm 0.6$  hours. (In adults with similar blood sampling, the half-life was  $3.7 \pm 1$  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  $\alpha$ ,  $\beta$ , and  $\gamma$ .

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. EC<sub>50</sub> values (50% effective concentrations) were in the range of  
524 0.003 to 15  $\mu$ M (1  $\mu$ M = 0.23 mcg/mL). HIV-1 from therapy-naïve subjects with no amino acid  
525 substitutions associated with resistance gave median EC<sub>50</sub> values of 0.429  $\mu$ M (range: 0.200 to  
526 2.007  $\mu$ M) from Virco (n = 92 baseline samples from COLA40263) and 2.35  $\mu$ M (1.37 to  
527 3.68  $\mu$ M) from Monogram Biosciences (n = 135 baseline samples from ESS30009). The EC<sub>50</sub>  
528 values of lamivudine against different HIV-1 clades (A-G) ranged from 0.001 to 0.120  $\mu$ M, and  
529 against HIV-2 isolates from 0.003 to 0.120  $\mu$ M in peripheral blood mononuclear cells. Ribavirin  
530 (50  $\mu$ 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  $\geq 400$  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  $4.9 \log_{10}$  copies/mL and  $4.6 \log_{10}$  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 log<sub>10</sub> copies/mL and  
591 4.83 log<sub>10</sub> 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/mm<sup>3</sup> (median = 122 cells/mm<sup>3</sup>) 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.

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%)

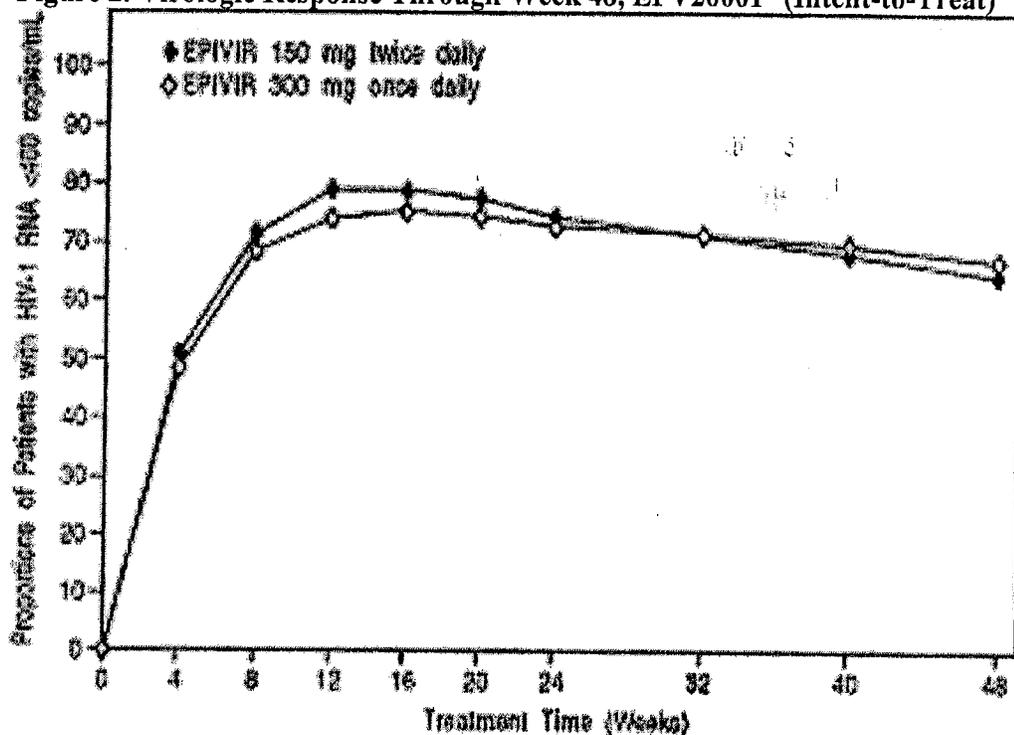
645 \* An investigational non-nucleoside reverse transcriptase inhibitor not approved in the United  
 646 States.

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/mm<sup>3</sup>  
660 (median = 362 cells/mm<sup>3</sup>), and median baseline plasma HIV-1 RNA of 4.66 log<sub>10</sub> 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<sup>††</sup>(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/mm<sup>3</sup> at Week 48 in patients receiving EPIVIR 300 mg once daily and 146 cells/mm<sup>3</sup> 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/mm<sup>3</sup>, median plasma HIV-1 RNA  
685 4.8 log<sub>10</sub> 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/mm<sup>3</sup> in the once-daily lamivudine group and 216 cells/mm<sup>3</sup> 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/mm<sup>3</sup> (mean: 1,060 cells/mm<sup>3</sup> and range: 0 to  
 702 4,650 cells/mm<sup>3</sup> for patients ≤5 years of age; mean: 419 cells/mm<sup>3</sup> and range: 0 to  
 703 1,555 cells/mm<sup>3</sup> for patients >5 years of age) and the mean baseline plasma HIV-1 RNA was  
 704 5.0 log<sub>10</sub> 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  
764 COMBIVIR, EPIVIR, EPIVIR-HBV, EPZICOM, and TRIZIVIR are registered trademarks of  
765 GlaxoSmithKline. ATRIPLA, EMTRIVA, and TRUVADA are trademarks of their respective  
766 owners and are not trademarks of GlaxoSmithKline. The makers of these brands are not  
767 affiliated with and do not endorse GlaxoSmithKline or its products.

768



GlaxoSmithKline

769

770 GlaxoSmithKline

771 Research Triangle Park, NC 27709

772

773 ©2008, GlaxoSmithKline. All rights reserved.