

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 for oral use

EPIVIR (lamivudine) 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 (2.2)

03/2015

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: 300 mg daily, administered as either 150 mg twice daily or 300 mg once daily. (2.1)
- Pediatric Patients Aged 3 Months and Older: Administered either once or twice daily. Dose should be calculated on body weight (kg) and should not exceed 300 mg daily. (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: 150 mg scored (3)
- Oral Solution: 10 mg per 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 alpha, 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 greater than or equal to 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 greater than or equal to 15%) in pediatric subjects were fever and cough. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact ViiV Healthcare at 1-877-844-8872 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

- Lactation: Breastfeeding not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 03/2015

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1 FULL PRESCRIBING INFORMATION

2 **WARNING: LACTIC ACIDOSIS, POSTTREATMENT EXACERBATIONS OF** 3 **HEPATITIS B IN CO-INFECTED PATIENTS, DIFFERENT FORMULATIONS OF** 4 **EPIVIR®.**

5 **Lactic Acidosis and Severe Hepatomegaly**

6 Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been
7 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 **Exacerbations of Hepatitis B**

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

18 **Important Differences among Lamivudine-containing Products**

19 EPIVIR tablets and oral solution (used to treat HIV-1 infection) contain a higher dose of
20 the active ingredient (lamivudine) than EPIVIR-HBV® tablets and oral solution (used to
21 treat chronic HBV infection). Patients with HIV-1 infection should receive only dosage
22 forms appropriate for treatment of HIV-1 [see *Warnings and Precautions (5.2)*].

23 **1 INDICATIONS AND USAGE**

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

27 **2 DOSAGE AND ADMINISTRATION**

28 **2.1 Adult Patients**

- 29 • The recommended oral dose of EPIVIR in HIV-1-infected adults is 300 mg daily,
30 administered as either 150 mg twice daily or 300 mg once daily, in combination with
31 other antiretroviral agents. If lamivudine is administered to a patient infected with HIV-1
32 and HBV, the dosage indicated for HIV-1 therapy should be used as part of an
33 appropriate combination regimen [see *Warnings and Precautions (5.2)*].
- 34 • EPIVIR may be taken with or without food.

35 **2.2 Pediatric Patients**

36 The recommended oral dose of EPIVIR oral solution in HIV-1-infected pediatric patients aged
37 3 months and older is 4 mg per kg twice daily or 8 mg per kg once daily (up to a maximum of
38 300 mg daily), administered in combination with other antiretroviral agents. Consider HIV-1
39 viral load and CD4+ cell count/percentage when selecting the dosing interval for patients
40 initiating treatment with oral solution [see *Clinical Pharmacology* (12.3)].

41 EPIVIR is also available as a scored tablet for HIV-1-infected pediatric patients who weigh at
42 least 14 kg and for whom a solid dosage form is appropriate. Before prescribing EPIVIR tablets,
43 children should be assessed for the ability to swallow tablets. If a child is unable to reliably
44 swallow EPIVIR tablets, the oral solution formulation should be prescribed. The recommended
45 oral dosage of EPIVIR tablets for HIV-1-infected pediatric patients is presented in Table 1.

46 **Table 1. Dosing Recommendations for EPIVIR Scored (150-mg) Tablets in Pediatric**
47 **Patients**

Weight (kg)	Once-daily Dosing Regimen ^a	Twice-daily Dosing Regimen Using Scored 150-mg Tablet		
		AM Dose	PM Dose	Total Daily Dose
14 to <20	1 tablet (150 mg)	½ tablet (75 mg)	½ tablet (75 mg)	150 mg
≥20 to <25	1½ tablets (225 mg)	½ tablet (75 mg)	1 tablet (150 mg)	225 mg
≥25	2 tablets (300 mg) ^b	1 tablet (150 mg)	1 tablet (150 mg)	300 mg

48 ^a Data regarding the efficacy of once-daily dosing is limited to subjects who transitioned from
49 twice-daily dosing to once-daily dosing after 36 weeks of treatment [see *Clinical Studies*
50 (14.2)].

51 ^b Patients may alternatively take one 300-mg tablet, which is not scored.

52 **2.3 Patients with Renal Impairment**

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

55 **Table 2. Adjustment of Dosage of EPIVIR in Adults and Adolescents (Greater than or**
56 **Equal to 25 kg) in 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

57 No additional dosing of EPIVIR is required after routine (4-hour) hemodialysis or peritoneal
58 dialysis.

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

62 **3 DOSAGE FORMS AND STRENGTHS**

63 **• EPIVIR Scored Tablets**

64 150 mg, are white, diamond-shaped, scored, film-coated tablets debossed with “GX CJ7” on
65 both sides.

66 **• EPIVIR Tablets**

67 300 mg, are gray, modified diamond-shaped, film-coated tablets engraved with “GX EJ7” on one
68 side and plain on the reverse side.

69 **• EPIVIR Oral Solution**

70 A clear, colorless to pale yellow, strawberry-banana flavored liquid, containing 10 mg of
71 lamivudine per 1 mL.

72 **4 CONTRAINDICATIONS**

73 EPIVIR tablets and oral solution are contraindicated in patients with previously demonstrated
74 clinically significant hypersensitivity (e.g., anaphylaxis) to any of the components of the
75 products.

76 **5 WARNINGS AND PRECAUTIONS**

77 **5.1 Lactic Acidosis/Severe Hepatomegaly with Steatosis**

78 Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported
79 with the use of nucleoside analogues alone or in combination, including lamivudine and other
80 antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside

81 exposure may be risk factors. Particular caution should be exercised when administering EPIVIR
82 to any patient with known risk factors for liver disease; however, cases also have been reported
83 in patients with no known risk factors. Treatment with EPIVIR should be suspended in any
84 patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced
85 hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked
86 transaminase elevations).

87 **5.2 Patients with HIV-1 and Hepatitis B Virus Co-infection**

88 Posttreatment Exacerbations of Hepatitis

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

100 Important Differences among Lamivudine-containing Products

101 EPIVIR tablets and oral solution contain a higher dose of the same active ingredient
102 (lamivudine) than EPIVIR-HBV tablets and EPIVIR-HBV oral solution. EPIVIR-HBV was
103 developed for patients with chronic hepatitis B. The formulation and dosage of lamivudine in
104 EPIVIR-HBV are not appropriate for patients co-infected with HIV-1 and HBV. Safety and
105 efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients
106 co-infected with HIV-1 and HBV. If treatment with EPIVIR-HBV is prescribed for chronic
107 hepatitis B for a patient with unrecognized or untreated HIV-1 infection, rapid emergence of
108 HIV-1 resistance is likely to result because of the subtherapeutic dose and the inappropriateness
109 of monotherapy HIV-1 treatment. If a decision is made to administer lamivudine to patients
110 co-infected with HIV-1 and HBV, EPIVIR tablets, EPIVIR oral solution, or another product
111 containing the higher dose of lamivudine should be used as part of an appropriate combination
112 regimen.

113 Emergence of Lamivudine-resistant HBV

114 In non-HIV-1-infected patients treated with lamivudine for chronic hepatitis B, emergence of
115 lamivudine-resistant HBV has been detected and has been associated with diminished treatment
116 response (see full prescribing information for EPIVIR-HBV for additional information).
117 Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been

118 reported in HIV-1-infected patients who have received lamivudine-containing antiretroviral
119 regimens in the presence of concurrent infection with hepatitis B virus.

120 **5.3 Use with Other Lamivudine- and Emtricitabine-containing Products**

121 EPIVIR is one of multiple lamivudine-containing products. Concomitant administration of
122 EPIVIR with other products containing lamivudine is not recommended. Concomitant use of
123 EPIVIR with emtricitabine-containing products is also not recommended.

124 **5.4 Use with Interferon- and Ribavirin-based Regimens**

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

137 **5.5 Pancreatitis**

138 In pediatric patients with a history of prior antiretroviral nucleoside exposure, a history of
139 pancreatitis, or other significant risk factors for the development of pancreatitis, EPIVIR should
140 be used with caution. Treatment with EPIVIR should be stopped immediately if clinical signs,
141 symptoms, or laboratory abnormalities suggestive of pancreatitis occur [*see Adverse Reactions*
142 (*6.1*)].

143 **5.6 Immune Reconstitution Syndrome**

144 Immune reconstitution syndrome has been reported in patients treated with combination
145 antiretroviral therapy, including EPIVIR. During the initial phase of combination antiretroviral
146 treatment, patients whose immune system responds may develop an inflammatory response to
147 indolent or residual opportunistic infections (such as *Mycobacterium avium* infection,
148 cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may
149 necessitate further evaluation and treatment.

150 Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome)
151 have also been reported to occur in the setting of immune reconstitution, however, the time to
152 onset is more variable, and can occur many months after initiation of treatment.

153 **5.7 Fat Redistribution**

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

159 **6 ADVERSE REACTIONS**

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

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

168 **6.1 Clinical Trials Experience in Adult Subjects**

169 Because clinical trials are conducted under widely varying conditions, adverse reaction rates
170 observed in the clinical trials of a drug cannot be directly compared with rates in the clinical
171 trials of another drug and may not reflect the rates observed in practice.

172 The safety profile of EPIVIR in adults is primarily based on 3,568 HIV-1-infected subjects in
173 7 clinical trials.

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

176 Selected clinical adverse reactions in greater than or equal to 5% of subjects during therapy with
177 EPIVIR 150 mg twice daily plus RETROVIR[®] 200 mg 3 times daily for up to 24 weeks are
178 listed in Table 3.

179 **Table 3. Selected Clinical Adverse Reactions (Greater than or Equal to 5% Frequency) in**
 180 **Four Controlled Clinical Trials (NUCA3001, NUCA3002, NUCB3001, NUCB3002)**

Adverse Reaction	EPIVIR 150 mg Twice Daily plus RETROVIR (n = 251)	RETROVIR^a (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%

181 ^a Either zidovudine monotherapy or zidovudine in combination with zalcitabine.

182 **Pancreatitis:** Pancreatitis was observed in 9 out of 2,613 adult subjects (0.3%) who received
 183 EPIVIR in controlled clinical trials EPV20001, NUCA3001, NUCB3001, NUCA3002,
 184 NUCB3002, and NUCB3007 [see *Warnings and Precautions (5.5)*].

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

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

189 **Table 4. Frequencies of Selected Grade 3-4 Laboratory Abnormalities in Adults in Four**
 190 **24-Week Surrogate Endpoint Trials (NUCA3001, NUCA3002, NUCB3001, NUCB3002)**
 191 **and a Clinical Endpoint Trial (NUCB3007)**

Test (Threshold Level)	24-Week Surrogate Endpoint Trials ^a		Clinical Endpoint Trial ^a	
	EPIVIR plus RETROVIR	RETROVIR ^b	EPIVIR plus Current Therapy ^c	Placebo plus Current Therapy ^c
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%

192 ^a The median duration on study was 12 months.

193 ^b Either zidovudine monotherapy or zidovudine in combination with zalcitabine.

194 ^c Current therapy was either zidovudine, zidovudine plus didanosine, or zidovudine plus
 195 zalcitabine.

196 ULN = Upper limit of normal.

197 ND = Not done.

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

201 **6.2 Clinical Trials Experience in Pediatric Subjects**

202 EPIVIR oral solution has been studied in 638 pediatric subjects aged 3 months to 18 years in
 203 3 clinical trials.

204 Selected clinical adverse reactions and physical findings with a greater than or equal to 5%
 205 frequency during therapy with EPIVIR 4 mg per kg twice daily plus RETROVIR 160 mg per m²
 206 3 times daily in therapy-naïve (less than or equal to 56 days of antiretroviral therapy) pediatric
 207 subjects are listed in Table 5.

208 **Table 5. Selected Clinical Adverse Reactions and Physical Findings (Greater than or Equal**
 209 **to 5% Frequency) in Pediatric Subjects in Trial 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 ^a	7%	6%
Nasal discharge or congestion	8%	11%
Other		
Skin rashes	12%	14%
Lymphadenopathy	9%	11%

210 ^a Includes pain, discharge, erythema, or swelling of an ear.

211 **Pancreatitis**

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

221 **Paresthesias and Peripheral Neuropathies**

222 Paresthesias and peripheral neuropathies were reported in 15 subjects (15%) in Trial
 223 NUCA2002, 6 subjects (9%) in Trial NUCA2005, and 2 subjects (less than 1%) in Trial
 224 ACTG300.

225 Selected laboratory abnormalities experienced by therapy-naive (less than or equal to 56 days of

226 antiretroviral therapy) pediatric subjects are listed in Table 6.

227 **Table 6. Frequencies of Selected Grade 3-4 Laboratory Abnormalities in Pediatric Subjects**
228 **in Trial 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%

229 ULN = Upper limit of normal.

230 Pediatric Subjects Once-daily vs Twice-daily Dosing (COL105677)

231 The safety of once-daily compared with twice-daily dosing of EPIVIR was assessed in the
232 ARROW trial. Primary safety assessment in the ARROW trial was based on Grade 3 and Grade
233 4 adverse events. The frequency of Grade 3 and 4 adverse events was similar among subjects
234 randomized to once-daily dosing compared with subjects randomized to twice-daily dosing. One
235 event of Grade 4 hepatitis in the once-daily cohort was considered as uncertain causality by the
236 investigator and all other Grade 3 or 4 adverse events were considered not related by the
237 investigator.

238 Neonates

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

252 **6.3 Postmarketing Experience**

253 The following adverse reactions have been identified during post-approval use of EPIVIR.

254 Because these reactions are reported voluntarily from a population of unknown size, it is not
255 always possible to reliably estimate their frequency or establish a causal relationship to drug
256 exposure. These reactions have been chosen for inclusion due to a combination of their
257 seriousness, frequency of reporting, or potential causal connection to lamivudine.

258 Body as a Whole

259 Redistribution/accumulation of body fat [*see Warnings and Precautions (5.7)*].

260 Endocrine and Metabolic

261 Hyperglycemia.

262 General

263 Weakness.

264 Hemic and Lymphatic

265 Anemia (including pure red cell aplasia and severe anemias progressing on therapy).

266 Hepatic and Pancreatic

267 Lactic acidosis and hepatic steatosis, posttreatment exacerbation of hepatitis B [*see Boxed*
268 *Warning, Warnings and Precautions (5.1, 5.2)*].

269 Hypersensitivity

270 Anaphylaxis, urticaria.

271 Musculoskeletal

272 Muscle weakness, CPK elevation, rhabdomyolysis.

273 Skin

274 Alopecia, pruritus.

275 **7 DRUG INTERACTIONS**

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

281 **7.1 Interferon- and Ribavirin-based Regimens**

282 Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of
283 HIV-1/HCV virologic suppression) was seen when ribavirin was coadministered with
284 lamivudine in HIV-1/HCV co-infected patients, hepatic decompensation (some fatal) has
285 occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for

286 HIV-1 and interferon alfa with or without ribavirin [see *Warnings and Precautions* (5.4),
287 *Clinical Pharmacology* (12.3)].

288 **7.2 Zalcitabine**

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

291 **7.3 Trimethoprim/Sulfamethoxazole (TMP/SMX)**

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

294 **7.4 Drugs with No Observed Interactions with EPIVIR**

295 A drug interaction trial showed no clinically significant interaction between EPIVIR and
296 zidovudine.

297 **8 USE IN SPECIFIC POPULATIONS**

298 **8.1 Pregnancy**

299 Pregnancy Exposure Registry

300 There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to
301 EPIVIR during pregnancy. Physicians are encouraged to register patients by calling the
302 Antiretroviral Pregnancy Registry at 1-800-258-4263.

303 Risk Summary

304 Available data from the Antiretroviral Pregnancy Registry show no difference in the risk of
305 overall major birth defects for lamivudine compared with the background rate for major birth
306 defects of 2.7% in the US reference population of the Metropolitan Atlanta Congenital Defects
307 Program (MACDP). Lamivudine produced embryonic toxicity in rabbits at a dose that produced
308 similar human exposures as the recommended clinical dose. The relevance of animal findings to
309 human pregnancy registry data is not known.

310 Data

311 *Human Data:* Based on prospective reports from the Antiretroviral Pregnancy Registry of over
312 11,000 exposures to lamivudine during pregnancy resulting in live births (including over 4,300
313 exposed in the first trimester), there was no difference between lamivudine and overall birth
314 defects compared with the background birth defect rate of 2.7% in the US reference population
315 of the MACDP. The prevalence of defects in the first trimester was 3.1% (95% CI: 2.6% to
316 3.7%).

317 Lamivudine pharmacokinetics were studied in pregnant women during 2 clinical trials conducted
318 in South Africa. The trials assessed pharmacokinetics in 16 women at 36 weeks gestation using
319 150 mg lamivudine twice daily with zidovudine, 10 women at 38 weeks gestation using 150 mg

320 lamivudine twice daily with zidovudine, and 10 women at 38 weeks gestation using lamivudine
321 300 mg twice daily without other antiretrovirals. These trials were not designed or powered to
322 provide efficacy information. Lamivudine pharmacokinetics in pregnant women were similar to
323 those seen in non-pregnant adults and in postpartum women. Lamivudine concentrations were
324 generally similar in maternal, neonatal, and umbilical cord serum samples. In a subset of
325 subjects, amniotic fluid specimens were collected following natural rupture of membranes and
326 confirmed that lamivudine crosses the placenta in humans. Amniotic fluid concentrations of
327 lamivudine were typically 2 times greater than maternal serum levels and ranged from 1.2 to
328 2.5 mcg per mL (150 mg twice daily) and 2.1 to 5.2 mcg per mL (300 mg twice daily).

329 *Animal Data:* Studies in pregnant rats showed that lamivudine is transferred to the fetus through
330 the placenta. Reproduction studies with orally administered lamivudine have been performed in
331 rats and rabbits at doses producing plasma levels up to approximately 35 times that for the
332 recommended adult HIV dose. No evidence of teratogenicity due to lamivudine was observed.
333 Evidence of embryo-lethality was seen in the rabbit at exposure levels similar to those observed
334 in humans but there was no indication of this effect in the rat at exposure levels up to 35 times
335 those in humans.

336 **8.2 Lactation**

337 Risk Summary

338 The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the
339 United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1
340 infection. Because of the potential for HIV-1 transmission mothers should be instructed not to
341 breastfeed.

342 **8.4 Pediatric Use**

343 The safety and effectiveness of EPIVIR in combination with other antiretroviral agents have
344 been established in pediatric patients aged 3 months and older [*see Dosage and Administration*
345 (2.2), *Adverse Reactions* (6.2), *Clinical Pharmacology* (12.3), *Clinical Studies* (14.2)].

346 **8.5 Geriatric Use**

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

354 **8.6 Patients with Impaired Renal Function**

355 Reduction of the dosage of EPIVIR is recommended for patients with impaired renal function

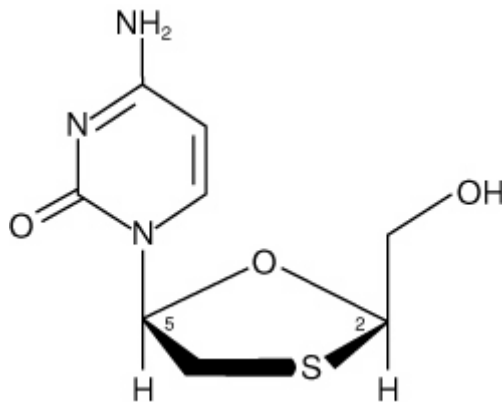
356 [see Dosage and Administration (2.3), Clinical Pharmacology (12.3)].

357 10 OVERDOSAGE

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

367 11 DESCRIPTION

368 EPIVIR (also known as 3TC) is a brand name for lamivudine, a synthetic nucleoside analogue
369 with activity against HIV-1 and HBV. The chemical name of lamivudine is (2R,cis)-4-amino-1-
370 (2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)enantiomer
371 of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2',3'-dideoxy, 3'-
372 thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.3. It has
373 the following structural formula:



374

375 Lamivudine is a white to off-white crystalline solid with a solubility of approximately 70 mg per
376 mL in water at 20°C.

377 EPIVIR tablets are for oral administration. Each scored 150-mg film-coated tablet contains
378 150 mg of lamivudine and the inactive ingredients hypromellose, magnesium stearate,
379 microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, and
380 titanium dioxide.

381 Each 300-mg film-coated tablet contains 300 mg of lamivudine and the inactive ingredients
382 black iron oxide, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene

383 glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide.

384 EPIVIR oral solution is for oral administration. One milliliter (1 mL) of EPIVIR oral solution
385 contains 10 mg of lamivudine (10 mg per mL) in an aqueous solution and the inactive
386 ingredients artificial strawberry and banana flavors, citric acid (anhydrous), methylparaben,
387 propylene glycol, propylparaben, sodium citrate (dihydrate), and sucrose (200 mg).

388 **12 CLINICAL PHARMACOLOGY**

389 **12.1 Mechanism of Action**

390 Lamivudine is an antiviral agent [*see Microbiology (12.4)*].

391 **12.3 Pharmacokinetics**

392 Pharmacokinetics in Adults

393 The pharmacokinetic properties of lamivudine have been studied in asymptomatic,
394 HIV-1-infected adult subjects after administration of single intravenous (IV) doses ranging from
395 0.25 to 8 mg per kg, as well as single and multiple (twice-daily regimen) oral doses ranging from
396 0.25 to 10 mg per kg.

397 The pharmacokinetic properties of lamivudine have also been studied as single and multiple oral
398 doses ranging from 5 mg to 600 mg per day administered to HBV-infected subjects.

399 The steady-state pharmacokinetic properties of the EPIVIR 300-mg tablet once daily for 7 days
400 compared with the EPIVIR 150-mg tablet twice daily for 7 days were assessed in a crossover
401 trial in 60 healthy subjects. EPIVIR 300 mg once daily resulted in lamivudine exposures that
402 were similar to EPIVIR 150 mg twice daily with respect to plasma $AUC_{24,ss}$; however, $C_{max,ss}$
403 was 66% higher and the trough value was 53% lower compared with the 150-mg twice-daily
404 regimen. Intracellular lamivudine triphosphate exposures in peripheral blood mononuclear cells
405 were also similar with respect to $AUC_{24,ss}$ and $C_{max24,ss}$; however, trough values were lower
406 compared with the 150-mg twice-daily regimen. Inter-subject variability was greater for
407 intracellular lamivudine triphosphate concentrations versus lamivudine plasma trough
408 concentrations.

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

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

418 **Effects of Food on Oral Absorption:** An investigational 25-mg dosage form of

419 lamivudine was administered orally to 12 asymptomatic, HIV-1-infected subjects on 2 occasions,
420 once in the fasted state and once with food (1,099 kcal; 75 grams fat, 34 grams protein, 72 grams
421 carbohydrate). Absorption of lamivudine was slower in the fed state (T_{\max} : 3.2 ± 1.3 hours)
422 compared with the fasted state (T_{\max} : 0.9 ± 0.3 hours); C_{\max} in the fed state was $40\% \pm 23\%$
423 (mean \pm SD) lower than in the fasted state. There was no significant difference in systemic
424 exposure (AUC_{∞}) in the fed and fasted states; therefore, EPIVIR tablets and oral solution may
425 be administered with or without food.

426 *Distribution:* The apparent volume of distribution after IV administration of lamivudine to
427 20 subjects was 1.3 ± 0.4 L per kg, suggesting that lamivudine distributes into extravascular
428 spaces. Volume of distribution was independent of dose and did not correlate with body weight.

429 Binding of lamivudine to human plasma proteins is low (less than 36%). In vitro studies showed
430 that over the concentration range of 0.1 to 100 mcg per mL, the amount of lamivudine associated
431 with erythrocytes ranged from 53% to 57% and was independent of concentration.

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

437 *Elimination:* The majority of lamivudine is eliminated unchanged in urine by active organic
438 cationic secretion. In 9 healthy subjects given a single 300-mg oral dose of lamivudine, renal
439 clearance was 199.7 ± 56.9 mL per min (mean \pm SD). In 20 HIV-1-infected subjects given a
440 single IV dose, renal clearance was 280.4 ± 75.2 mL per min (mean \pm SD), representing
441 $71\% \pm 16\%$ (mean \pm SD) of total clearance of lamivudine.

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

447 Special Populations

448 *Renal Impairment:* The pharmacokinetic properties of lamivudine have been determined in a
449 small group of HIV-1-infected adults with impaired renal function (Table 7).

450 **Table 7. Pharmacokinetic Parameters (Mean ± SD) after a Single 300-mg Oral Dose of**
 451 **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•h/mL)	11.0 ± 1.7	48.0 ± 19	157 ± 74
Cl/F (mL/min)	464 ± 76	114 ± 34	36 ± 11

452 Exposure (AUC_∞), C_{max}, and half-life increased with diminishing renal function (as expressed
 453 by creatinine clearance). Apparent total oral clearance (Cl/F) of lamivudine decreased as
 454 creatinine clearance decreased. T_{max} was not significantly affected by renal function. Based on
 455 these observations, it is recommended that the dosage of lamivudine be modified in patients with
 456 renal impairment [see Dosage and Administration (2.3)].

457 Based on a trial in otherwise healthy subjects with impaired renal function, hemodialysis
 458 increased lamivudine clearance from a mean of 64 to 88 mL per min; however, the length of time
 459 of hemodialysis (4 hours) was insufficient to significantly alter mean lamivudine exposure after a
 460 single-dose administration. Continuous ambulatory peritoneal dialysis and automated peritoneal
 461 dialysis have negligible effects on lamivudine clearance. Therefore, it is recommended,
 462 following correction of dose for creatinine clearance, that no additional dose modification be
 463 made after routine hemodialysis or peritoneal dialysis.

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

465 The effects of renal impairment on lamivudine pharmacokinetics in pediatric patients are not
 466 known.

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

472 **Pediatric Patients:** The pharmacokinetics of lamivudine have been studied after either single or
 473 repeat doses of EPIVIR in 210 pediatric subjects. Pediatric subjects receiving lamivudine oral
 474 solution according to the recommended dosage regimen achieved approximately 25% lower
 475 plasma concentrations of lamivudine compared with HIV-1-infected adults. Pediatric subjects
 476 receiving lamivudine oral tablets achieved plasma concentrations comparable to or slightly
 477 higher than those observed in adults. The absolute bioavailability of both EPIVIR tablets and
 478 oral solution are lower in children than adults. The relative bioavailability of EPIVIR oral
 479 solution is approximately 40% lower than tablets containing lamivudine in pediatric subjects

480 despite no difference in adults. The mechanisms for the diminished absolute bioavailability of
 481 lamivudine and relative bioavailability of lamivudine solution are unknown.

482 The pharmacokinetics of lamivudine dosed once daily in HIV-1-infected pediatric subjects aged
 483 3 months through 12 years was evaluated in 3 trials (PENTA-15 [n = 17], PENTA 13 [n = 19],
 484 and ARROW PK [n = 35]). All 3 trials were 2-period, crossover, open-label pharmacokinetic
 485 trials of twice- versus once-daily dosing of abacavir and lamivudine. These 3 trials demonstrated
 486 that once-daily dosing provides similar AUC₀₋₂₄ to twice-daily dosing of lamivudine at the same
 487 total daily dose when comparing the dosing regimens within the same formulation (i.e., either the
 488 oral solution or the tablet formulation). The mean C_{max} was approximately 80% to 90% higher
 489 with lamivudine once-daily dosing compared with twice-daily dosing.

490 **Table 8. Pharmacokinetic Parameters (Geometric Mean [95% CI]) after Repeat Dosing of**
 491 **Lamivudine in 3 Pediatric Trials**

	Trial (Number of Subjects)					
	ARROW PK (n = 35)		PENTA-13 (n = 19)		PENTA-15 (n = 17) ^a	
Age Range	3-12 years		2-12 years		3-36 months	
Formulation	Tablet		Solution and Tablet ^b		Solution	
Parameter	Once Daily	Twice Daily	Once Daily	Twice Daily	Once Daily	Twice Daily
C _{max} (mcg/mL)	3.17 (2.76, 3.64)	1.80 (1.59, 2.04)	2.09 (1.80, 2.42)	1.11 (0.96, 1.29)	1.87 (1.65, 2.13)	1.05 (0.88, 1.26)
AUC ₍₀₋₂₄₎ (mcg•h/mL)	13.0 (11.4, 14.9)	12.0 (10.7, 13.4)	9.80 (8.64, 11.1)	8.88 (7.67, 10.3)	8.66 (7.46, 10.1)	9.48 (7.89, 11.4)

492 ^a N = 16 for PENTA-15 C_{max}.

493 ^b Five subjects in PENTA-13 received lamivudine tablets.

494 Distribution of lamivudine into cerebrospinal fluid (CSF) was assessed in 38 pediatric subjects
 495 after multiple oral dosing with lamivudine. CSF samples were collected between 2 and 4 hours
 496 postdose. At the dose of 8 mg per kg per day, CSF lamivudine concentrations in 8 subjects
 497 ranged from 5.6% to 30.9% (mean ± SD of 14.2% ± 7.9%) of the concentration in a
 498 simultaneous serum sample, with CSF lamivudine concentrations ranging from 0.04 to 0.3 mcg
 499 per mL.

500 Limited, uncontrolled pharmacokinetic and safety data are available from administration of
 501 lamivudine (and zidovudine) to 36 infants aged up to 1 week in 2 trials in South Africa. In these
 502 trials, lamivudine clearance was substantially reduced in 1-week-old neonates relative to
 503 pediatric subjects (aged over 3 months) studied previously. There is insufficient information to
 504 establish the time course of changes in clearance between the immediate neonatal period and the

505 age-ranges over 3 months old [see *Adverse Reactions (6.2)*].

506 *Geriatric Patients:* The pharmacokinetics of lamivudine after administration of EPIVIR to
507 subjects over 65 years have not been studied [see *Use in Specific Populations (8.5)*].

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

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

510 Drug Interactions

511 *Interferon Alfa:* There was no significant pharmacokinetic interaction between lamivudine and
512 interferon alfa in a trial of 19 healthy male subjects [see *Warnings and Precautions (5.4)*].

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

519 *Trimethoprim/Sulfamethoxazole:* Lamivudine and TMP/SMX were coadministered to
520 14 HIV-1-positive subjects in a single-center, open-label, randomized, crossover trial. Each
521 subject received treatment with a single 300-mg dose of lamivudine and TMP 160 mg/SMX
522 800 mg once a day for 5 days with concomitant administration of lamivudine 300 mg with the
523 fifth dose in a crossover design. Coadministration of TMP/SMX with lamivudine resulted in an
524 increase of 43% ± 23% (mean ± SD) in lamivudine AUC_∞, a decrease of 29% ± 13% in
525 lamivudine oral clearance, and a decrease of 30% ± 36% in lamivudine renal clearance. The
526 pharmacokinetic properties of TMP and SMX were not altered by coadministration with
527 lamivudine [see *Drug Interactions (7.3)*].

528 *Zidovudine:* No clinically significant alterations in lamivudine or zidovudine pharmacokinetics
529 were observed in 12 asymptomatic HIV-1-infected adult subjects given a single dose of
530 zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg every 12 h) [see
531 *Drug Interactions (7.4)*].

532 **12.4 Microbiology**

533 Mechanism of Action

534 Intracellularly, lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine
535 triphosphate (3TC-TP). The principal mode of action of 3TC-TP is the inhibition of HIV-1
536 reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide
537 analogue into viral DNA. 3TC-TP is a weak inhibitor of mammalian DNA polymerases α, β, and
538 γ.

539 Antiviral Activity

540 The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines
541 (including monocytes and fresh human peripheral blood lymphocytes) using standard
542 susceptibility assays. EC₅₀ values (50% effective concentrations) were in the range of 0.003 to
543 15 μM (1 μM = 0.23 mcg per mL). HIV-1 from therapy-naive subjects with no amino acid
544 substitutions associated with resistance gave median EC₅₀ values of 0.429 μM (range: 0.200 to
545 2.007 μM) from Virco (n = 92 baseline samples from COLA40263) and 2.35 μM (range: 1.37 to
546 3.68 μM) from Monogram Biosciences (n = 135 baseline samples from ESS30009). The EC₅₀
547 values of lamivudine against different HIV-1 clades (A-G) ranged from 0.001 to 0.120 μM, and
548 against HIV-2 isolates from 0.003 to 0.120 μM in peripheral blood mononuclear cells. Ribavirin
549 (50 μM) decreased the anti-HIV-1 activity of lamivudine by 3.5 fold in MT-4 cells. In
550 HIV-1-infected MT-4 cells, lamivudine in combination with zidovudine at various ratios
551 exhibited synergistic antiretroviral activity. Please see the full prescribing information for
552 EPIVIR-HBV for information regarding the inhibitory activity of lamivudine against HBV.

553 Resistance

554 Lamivudine-resistant variants of HIV-1 have been selected in cell culture. Genotypic analysis
555 showed that the resistance was due to a specific amino acid substitution in the HIV-1 reverse
556 transcriptase at codon 184 changing the methionine to either isoleucine or valine (M184V/I).

557 HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from subjects.
558 Susceptibility of clinical isolates to lamivudine and zidovudine was monitored in controlled
559 clinical trials. In subjects receiving lamivudine monotherapy or combination therapy with
560 lamivudine plus zidovudine, HIV-1 isolates from most subjects became phenotypically and
561 genotypically resistant to lamivudine within 12 weeks. In some subjects harboring
562 zidovudine-resistant virus at baseline, phenotypic sensitivity to zidovudine was restored by
563 12 weeks of treatment with lamivudine and zidovudine. Combination therapy with lamivudine
564 plus zidovudine delayed the emergence of mutations conferring resistance to zidovudine.

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

573 Cross-resistance

574 Lamivudine-resistant HIV-1 mutants were cross-resistant to didanosine (ddI) and zalcitabine
575 (ddC). In some subjects treated with zidovudine plus didanosine or zalcitabine, isolates resistant
576 to multiple reverse transcriptase inhibitors, including lamivudine, have emerged.

577 Genotypic and Phenotypic Analysis of On-therapy HIV-1 Isolates from Subjects with
578 Virologic Failure

579 *Trial EPV20001*: Fifty-three of 554 (10%) subjects enrolled in EPV20001 were identified as
580 virological failures (plasma HIV-1 RNA level greater than or equal to 400 copies per mL) by
581 Week 48. Twenty-eight subjects were randomized to the lamivudine once-daily treatment group
582 and 25 to the lamivudine twice-daily treatment group. The median baseline plasma HIV-1 RNA
583 levels of subjects in the lamivudine once-daily group and lamivudine twice-daily group were
584 4.9 log₁₀ copies per mL and 4.6 log₁₀ copies per mL, respectively.

585 Genotypic analysis of on-therapy isolates from 22 subjects identified as virologic failures in the
586 lamivudine once-daily group showed that isolates from 0 of 22 subjects contained
587 treatment-emergent amino acid substitutions associated with zidovudine resistance (M41L,
588 D67N, K70R, L210W, T215Y/F, or K219Q/E), isolates from 10 of 22 subjects contained
589 treatment-emergent amino acid substitutions associated with efavirenz resistance (L100I, K101E,
590 K103N, V108I, or Y181C), and isolates from 8 of 22 subjects contained a treatment-emergent
591 lamivudine resistance-associated substitution (M184I or M184V).

592 Genotypic analysis of on-therapy isolates from subjects (n = 22) in the lamivudine twice-daily
593 treatment group showed that isolates from 1 of 22 subjects contained treatment-emergent
594 zidovudine resistance substitutions, isolates from 7 of 22 contained treatment-emergent efavirenz
595 resistance substitutions, and isolates from 5 of 22 contained treatment-emergent lamivudine
596 resistance substitutions.

597 Phenotypic analysis of baseline-matched on-therapy HIV-1 isolates from subjects (n = 13)
598 receiving lamivudine once daily showed that isolates from 12 of 13 subjects were susceptible to
599 zidovudine; isolates from 8 of 13 subjects exhibited a 25- to 295-fold decrease in susceptibility
600 to efavirenz, and isolates from 7 of 13 subjects showed an 85- to 299-fold decrease in
601 susceptibility to lamivudine.

602 Phenotypic analysis of baseline-matched on-therapy HIV-1 isolates from subjects (n = 13)
603 receiving lamivudine twice daily showed that isolates from all 13 subjects were susceptible to
604 zidovudine; isolates from 3 of 13 subjects exhibited a 21- to 342-fold decrease in susceptibility
605 to efavirenz, and isolates from 4 of 13 subjects exhibited a 29- to 159-fold decrease in
606 susceptibility to lamivudine.

607 *Trial EPV40001*: Fifty subjects received zidovudine 300 mg twice daily plus abacavir 300 mg
608 twice daily plus lamivudine 300 mg once daily and 50 subjects received zidovudine 300 mg plus
609 abacavir 300 mg plus lamivudine 150 mg all twice-daily. The median baseline plasma HIV-1
610 RNA levels for subjects in the 2 groups were 4.79 log₁₀ copies per mL and 4.83 log₁₀ copies per
611 mL, respectively. Fourteen of 50 subjects in the lamivudine once-daily treatment group and 9 of
612 50 subjects in the lamivudine twice-daily group were identified as virologic failures.

613 Genotypic analysis of on-therapy HIV-1 isolates from subjects (n = 9) in the lamivudine

614 once-daily treatment group showed that isolates from 6 subjects had an abacavir and/or
615 lamivudine resistance-associated substitution M184V alone. On-therapy isolates from subjects
616 (n = 6) receiving lamivudine twice daily showed that isolates from 2 subjects had M184V alone,
617 and isolates from 2 subjects harbored the M184V substitution in combination with zidovudine
618 resistance-associated amino acid substitutions.

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

622 Phenotypic analysis of on-therapy isolates from subjects (n = 4) receiving lamivudine twice daily
623 showed that HIV-1 isolates from 1 subject exhibited a 45-fold decrease in susceptibility to
624 lamivudine and a 4.5-fold decrease in susceptibility to zidovudine.

625 **13 NONCLINICAL TOXICOLOGY**

626 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

627 Carcinogenesis

628 Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of
629 carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) those observed in
630 humans at the recommended therapeutic dose for HIV-1 infection.

631 Mutagenesis

632 Lamivudine was not active in a microbial mutagenicity screen or an in vitro cell transformation
633 assay, but showed weak in vitro mutagenic activity in a cytogenetic assay using cultured human
634 lymphocytes and in the mouse lymphoma assay. However, lamivudine showed no evidence of in
635 vivo genotoxic activity in the rat at oral doses of up to 2,000 mg per kg, producing plasma levels
636 of 35 to 45 times those in humans at the recommended dose for HIV-1 infection.

637 Impairment of Fertility

638 In a study of reproductive performance, lamivudine administered to rats at doses up to 4,000 mg
639 per kg per day, producing plasma levels 47 to 70 times those in humans, revealed no evidence of
640 impaired fertility and no effect on the survival, growth, and development to weaning of the
641 offspring.

642 **14 CLINICAL STUDIES**

643 The use of EPIVIR is based on the results of clinical trials in HIV-1-infected subjects in
644 combination regimens with other antiretroviral agents. Information from trials with clinical
645 endpoints or a combination of CD4+ cell counts and HIV-1 RNA measurements is included
646 below as documentation of the contribution of lamivudine to a combination regimen in
647 controlled trials.

648 **14.1 Adult Subjects**

649 Clinical Endpoint Trial

650 NUCB3007 (CAESAR) was a multi-center, double-blind, placebo-controlled trial comparing
651 continued current therapy (zidovudine alone [62% of subjects] or zidovudine with didanosine or
652 zalcitabine [38% of subjects]) to the addition of EPIVIR or EPIVIR plus an investigational
653 non-nucleoside reverse transcriptase inhibitor (NNRTI), randomized 1:2:1. A total of
654 1,816 HIV-1-infected adults with 25 to 250 CD4+ cells per mm³ (median = 122 cells per mm³) at
655 baseline were enrolled: median age was 36 years, 87% were male, 84% were
656 nucleoside-experienced, and 16% were therapy-naive. The median duration on trial was
657 12 months. Results are summarized in Table 9.

658 **Table 9. Number of Subjects (%) with at Least One HIV-1 Disease Progression Event or**
659 **Death**

Endpoint	Current Therapy (n = 460)	EPIVIR plus Current Therapy (n = 896)	EPIVIR plus an NNRTI^a 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%)

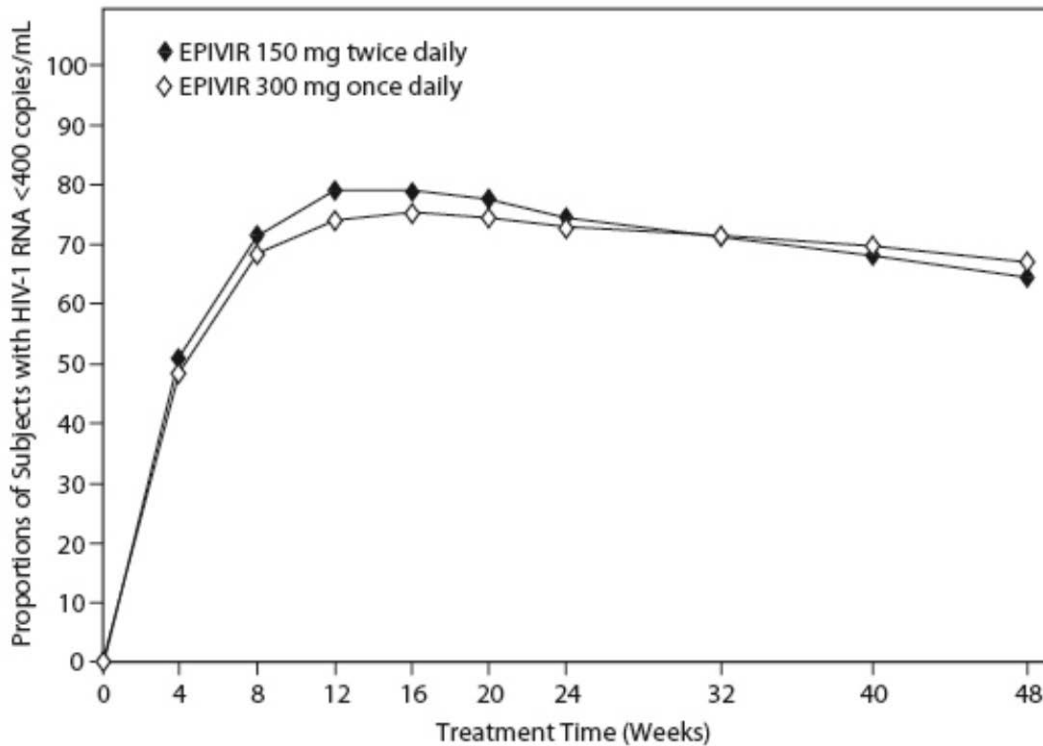
660 ^a An investigational non-nucleoside reverse transcriptase inhibitor not approved in the United
661 States.

662 Surrogate Endpoint Trials

663 *Dual Nucleoside Analogue Trials:* Principal clinical trials in the initial development of
664 lamivudine compared lamivudine/zidovudine combinations with zidovudine monotherapy or
665 with zidovudine plus zalcitabine. These trials demonstrated the antiviral effect of lamivudine in a
666 2-drug combination. More recent uses of lamivudine in treatment of HIV-1 infection incorporate
667 it into multiple-drug regimens containing at least 3 antiretroviral drugs for enhanced viral
668 suppression.

669 *Dose Regimen Comparison Surrogate Endpoint Trials in Therapy-naive Adults:*
670 EPV20001 was a multi-center, double-blind, controlled trial in which subjects were randomized
671 1:1 to receive EPIVIR 300 mg once daily or EPIVIR 150 mg twice daily, in combination with
672 zidovudine 300 mg twice daily and efavirenz 600 mg once daily. A total of 554 antiretroviral
673 treatment-naive HIV-1-infected adults enrolled: male (79%), white (50%), median age of
674 35 years, baseline CD4+ cell counts of 69 to 1,089 cells per mm³ (median = 362 cells per mm³),
675 and median baseline plasma HIV-1 RNA of 4.66 log₁₀ copies per mL. Outcomes of treatment
676 through 48 weeks are summarized in Figure 1 and Table 10.

677 **Figure 1. Virologic Response through Week 48, EPV20001^{ab} (Intent-to-Treat)**



678

679 ^a Roche AMPLICOR HIV-1 MONITOR.

680 ^b Responders at each visit are subjects who had achieved and maintained HIV-1 RNA less than
681 400 copies per mL without discontinuation by that visit.

682 **Table 10. 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 ^a	67%	65%
Virologic failure ^b	8%	8%
Discontinued due to clinical progression	<1%	0%
Discontinued due to adverse events	6%	12%
Discontinued due to other reasons ^c	18%	14%

683 ^a Achieved confirmed plasma HIV-1 RNA less than 400 copies per mL and maintained through
684 48 weeks.

685 ^b Achieved suppression but rebounded by Week 48, discontinued due to virologic failure,
686 insufficient viral response according to the investigator, or never suppressed through Week 48.

687 ^c Includes consent withdrawn, lost to follow-up, protocol violation, data outside the trial-defined

688 schedule, and randomized but never initiated treatment.

689 The proportions of subjects with HIV-1 RNA less than 50 copies per mL (via Roche
690 Ultrasensitive assay) through Week 48 were 61% for subjects receiving EPIVIR 300 mg once
691 daily and 63% for subjects receiving EPIVIR 150 mg twice daily. Median increases in CD4+ cell
692 counts were 144 cells per mm³ at Week 48 in subjects receiving EPIVIR 300 mg once daily and
693 146 cells per mm³ for subjects receiving EPIVIR 150 mg twice daily.

694 A small, randomized, open-label pilot trial, EPV40001, was conducted in Thailand. A total of
695 159 treatment-naïve adult subjects (male 32%, Asian 100%, median age 30 years, baseline
696 median CD4+ cell count 380 cells per mm³, median plasma HIV-1 RNA 4.8 log₁₀ copies per mL)
697 were enrolled. Two of the treatment arms in this trial provided a comparison between lamivudine
698 300 mg once daily (n = 54) and lamivudine 150 mg twice daily (n = 52), each in combination
699 with zidovudine 300 mg twice daily and abacavir 300 mg twice daily. In intent-to-treat analyses
700 of 48-week data, the proportions of subjects with HIV-1 RNA below 400 copies per mL were
701 61% (33 of 54) in the group randomized to once-daily lamivudine and 75% (39 of 52) in the
702 group randomized to receive all 3 drugs twice daily; the proportions with HIV-1 RNA below
703 50 copies per mL were 54% (29 of 54) in the once-daily lamivudine group and 67% (35 of 52) in
704 the all-twice-daily group; and the median increases in CD4+ cell counts were 166 cells per mm³
705 in the once-daily lamivudine group and 216 cells per mm³ in the all-twice-daily group.

706 **14.2 Pediatric Subjects**

707 Clinical Endpoint Trial

708 ACTG300 was a multi-center, randomized, double-blind trial that provided for comparison of
709 EPIVIR plus RETROVIR (zidovudine) with didanosine monotherapy. A total of
710 471 symptomatic, HIV-1-infected therapy-naïve (less than or equal to 56 days of antiretroviral
711 therapy) pediatric subjects were enrolled in these 2 treatment arms. The median age was
712 2.7 years (range: 6 weeks to 14 years), 58% were female, and 86% were non-white. The mean
713 baseline CD4+ cell count was 868 cells per mm³ (mean: 1,060 cells per mm³ and range: 0 to
714 4,650 cells per mm³ for subjects aged less than or equal to 5 years; mean: 419 cells per mm³ and
715 range: 0 to 1,555 cells per mm³ for subjects aged over 5 years) and the mean baseline plasma
716 HIV-1 RNA was 5.0 log₁₀ copies per mL. The median duration on trial was 10.1 months for the
717 subjects receiving EPIVIR plus RETROVIR and 9.2 months for subjects receiving didanosine
718 monotherapy. Results are summarized in Table 11.

719 **Table 11. Number of Subjects (%) Reaching a Primary Clinical Endpoint (Disease**
 720 **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%)

721 Once-daily Dosing

722 ARROW (COL105677) was a 5-year randomized, multicenter trial which evaluated multiple
 723 aspects of clinical management of HIV-1 infection in pediatric subjects. HIV-1-infected,
 724 treatment-naïve subjects aged 3 months to 17 years were enrolled and treated with a first-line
 725 regimen containing EPIVIR and abacavir, dosed twice daily according to World Health
 726 Organization recommendations. After a minimum of 36 weeks on treatment, subjects were given
 727 the option to participate in Randomization 3 of the ARROW trial, comparing the safety and
 728 efficacy of once-daily dosing with twice-daily dosing of EPIVIR and abacavir, in combination
 729 with a third antiretroviral drug, for an additional 96 weeks. Of the 1,206 original ARROW
 730 subjects, 669 participated in Randomization 3. Virologic suppression was not a requirement for
 731 participation: at baseline for Randomization 3 (following a minimum of 36 weeks of twice-daily
 732 treatment), 75% of subjects in the twice-daily cohort were virologically suppressed, compared
 733 with 71% of subjects in the once-daily cohort.

734 The proportion of subjects with HIV-1 RNA of less than 80 copies per mL through 96 weeks is
 735 shown in Table 12. The differences between virologic responses in the two treatment arms were
 736 comparable across baseline characteristics for gender and age.

737 **Table 12. Virologic Outcome of Randomized Treatment at Week 96^a (ARROW**
 738 **Randomization 3)**

Outcome	EPIVIR plus Abacavir Twice-daily Dosing (n = 333)	EPIVIR plus Abacavir Once-daily Dosing (n = 336)
HIV-1 RNA <80 copies/mL^b	70%	67%
HIV-1 RNA ≥80 copies/mL^c	28%	31%
No virologic data		
Discontinued due to adverse event or death	1%	<1%
Discontinued study for other reasons ^d	0%	<1%
Missing data during window but on study	1%	1%

739 ^a Analyses were based on the last observed viral load data within the Week 96 window.

740 ^b Predicted difference (95% CI) of response rate is -4.5% (-11% to 2%) at Week 96.

741 ^c Includes subjects who discontinued due to lack or loss of efficacy or for reasons other than an
 742 adverse event or death, and had a viral load value of greater than or equal to 80 copies per mL,
 743 or subjects who had a switch in background regimen that was not permitted by the protocol.

744 ^d Other includes reasons such as withdrew consent, loss to follow-up, etc. and the last available
 745 HIV-1 RNA less than 80 copies per mL (or missing).

746 **16 HOW SUPPLIED/STORAGE AND HANDLING**

747 **EPIVIR Scored Tablets, 150 mg**

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

749 Bottle of 60 tablets (NDC 49702-203-18) with child-resistant closure.

750 **EPIVIR Tablets, 300 mg**

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

753 Bottle of 30 tablets (NDC 49702-204-13) with child-resistant closure.

754 Recommended Storage:

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

757 **EPIVIR Oral Solution, 10 mg per mL**

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

760 Plastic bottle of 240 mL (NDC 49702-205-48) with child-resistant closure. This product does not
 761 require reconstitution.

762 Recommended Storage:
763 Store in tightly closed bottles at 25°C (77°F) [see USP Controlled Room Temperature].

764 **17 PATIENT COUNSELING INFORMATION**

765 Advise the patient to read the FDA-approved patient labeling (Patient Information).

766 Lactic Acidosis/Hepatomegaly

767 Inform patients that some HIV medicines, including EPIVIR, can cause a rare, but serious
768 condition called lactic acidosis with liver enlargement (hepatomegaly) [see *Warnings and*
769 *Precautions (5.1)*].

770 HIV-1/HBV Co-infection

771 Inform patients co-infected with HIV-1 and HBV that deterioration of liver disease has occurred
772 in some cases when treatment with lamivudine was discontinued. Advise patients to discuss any
773 changes in regimen with their physician [see *Warnings and Precautions (5.2)*].

774 Differences in Formulations of EPIVIR

775 Advise patients that EPIVIR tablets and oral solution contain a higher dose of the same active
776 ingredient (lamivudine) as EPIVIR-HBV tablets and oral solution. If a decision is made to
777 include lamivudine in the HIV-1 treatment regimen of a patient co-infected with HIV-1 and
778 HBV, the formulation and dosage of lamivudine in EPIVIR (not EPIVIR-HBV) should be used
779 [see *Warnings and Precautions (5.2)*].

780 Use with Other Lamivudine- and Emtricitabine-containing Products

781 EPIVIR should not be coadministered with drugs containing lamivudine or emtricitabine,
782 including COMBIVIR (lamivudine/zidovudine) tablets, EPZICOM (abacavir sulfate and
783 lamivudine) tablets, TRIUMEQ (dolutegravir, abacavir, lamivudine), TRIZIVIR (abacavir
784 sulfate, lamivudine, and zidovudine), ATRIPLA (efavirenz, emtricitabine, and tenofovir),
785 EMTRIVA (emtricitabine), STRIBILD (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil
786 fumarate), TRUVADA (emtricitabine and tenofovir), or COMPLERA
787 (rilpivirine/emtricitabine/tenofovir) [see *Warnings and Precautions (5.3)*].

788 HIV-1/HCV Co-infection:

789 Inform patients with HIV-1/HCV co-infection that hepatic decompensation (some fatal) has
790 occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for
791 HIV-1 and interferon alfa with or without ribavirin [see *Warnings and Precautions (5.4)*].

792 Risk of Pancreatitis

793 Advise parents or guardians to monitor pediatric patients for signs and symptoms of pancreatitis
794 [see *Warnings and Precautions (5.5)*].

795 Redistribution/Accumulation of Body Fat

796 Inform patients that redistribution or accumulation of body fat may occur in patients receiving
797 antiretroviral therapy, including EPIVIR, and that the cause and long-term health effects of these
798 conditions are not known at this time [see Warnings and Precautions (5.7)].

799 Sucrose Content of EPIVIR Oral Solution

800 Advise diabetic patients that each 15-mL dose of EPIVIR oral solution contains 3 grams of
801 sucrose (1 mL = 200 mg of sucrose) [see Description (11)].

802 Information about HIV-1 Infection

803 EPIVIR is not a cure for HIV-1 infection and patients may continue to experience illnesses
804 associated with HIV-1 infection, including opportunistic infections. Patients must remain on
805 continuous HIV therapy to control HIV-1 infection and decrease HIV-related illness. Patients
806 should be told that sustained decreases in plasma HIV-1 RNA have been associated with a
807 reduced risk of progression to AIDS and death. Patients should remain under the care of a
808 physician when using EPIVIR.

809 Patients should be informed to take all HIV medications exactly as prescribed. If you miss a dose
810 of EPIVIR, take it as soon as you remember. Do not take 2 doses at the same time. If you are not
811 sure about your dosing, call your healthcare provider.

812 Patients should be advised to avoid doing things that can spread HIV-1 infection to others.

- 813 • **Do not re-use or share needles or other injection equipment.**
- 814 • **Do not share personal items that can have blood or body fluids on them, like**
815 **toothbrushes and razor blades.**
- 816 • Continue to practice safer sex by using a latex or polyurethane condom or other barrier
817 method to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- 818 • Female patients should be advised not to breastfeed. Mothers with HIV-1 should not
819 breastfeed because HIV-1 can be passed to the baby in the breast milk.

820

821 COMBIVIR, EPIVIR, EPZICOM, TRIUMEQ, RETROVIR, and TRIZIVIR are registered
822 trademarks of the ViiV Healthcare group of companies.

823 EPIVIR-HBV is a registered trademark of the GSK group of companies.

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825 ViiV Healthcare group of companies. The makers of these brands are not affiliated with and do
826 not endorse the ViiV Healthcare group of companies or its products.

827

828

829 Manufactured for:



830
831 ViiV Healthcare
832 Research Triangle Park, NC 27709

833
834 by:



835
836 GlaxoSmithKline
837 Research Triangle Park, NC 27709

838
839 Manufactured under agreement from
840 **Shire Pharmaceuticals Group plc**
841 Basingstoke, UK

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843 EPV:XPI
844

PATIENT INFORMATION

**EPIVIR® (EP-i-veer)
(lamivudine)
tablets**

**EPIVIR (EP-i-veer)
(lamivudine)
oral solution**

What is the most important information I should know about EPIVIR?

EPIVIR can cause serious side effects, including:

- **Build-up of an acid in your blood (lactic acidosis).** Lactic acidosis can happen in some people who take EPIVIR or similar medicines (nucleoside analogs). Lactic acidosis is a serious medical emergency that can lead to death. Lactic acidosis can be hard to identify early because the symptoms could seem like symptoms of other health problems. **Call your healthcare provider right away if you get any of the following symptoms that could be signs of lactic acidosis:**

- feel very weak or tired
- unusual (not normal) muscle pain
- trouble breathing
- stomach pain with nausea and vomiting
- feel cold, especially in your arms and legs
- feel dizzy or light-headed
- have a fast or irregular heartbeat

- **Severe liver problems.** Severe liver problems can happen in people who take EPIVIR or similar medicines. In some cases these liver problems can lead to death. Your liver may become large (hepatomegaly) and you may develop fat in your liver (steatosis) when you take EPIVIR. **Call your healthcare provider right away if you get any of the following signs of liver problems:**

- your skin or the white part of your eyes turns yellow (jaundice)
- dark or “tea-colored” urine
- light-colored stools (bowel movements)
- loss of appetite for several days or longer
- nausea
- pain, aching, or tenderness on the right side of your stomach area

You may be more likely to get lactic acidosis or severe liver problems if you are female, very overweight (obese), or have been taking nucleoside analog medicines for a long time or have risks for liver problems.

- **Worsening of hepatitis B infection.** If you have HIV-1 (Human Immunodeficiency Virus) and hepatitis B virus (HBV) infection, your HBV may get worse (flare-up) if you stop taking EPIVIR. A “flare-up” is when your HBV infection suddenly returns in a worse way than before. Worsening liver disease from HBV can be serious and may lead to death.
 - Do not run out of EPIVIR. Refill your prescription or talk to your healthcare provider

- 870 before your EPIVIR is all gone.
- 871 • Do not stop EPIVIR without first talking to your healthcare provider.
 - 872 • If you stop taking EPIVIR, your healthcare provider will need to check your health often
 - 873 and do blood tests regularly for several months to check your liver.

874 **What is EPIVIR?**

875 EPIVIR is a prescription HIV-1 medicine used with other antiretroviral medicines to treat HIV-1
876 infections in adults and children aged 3 months and older. HIV-1 is the virus that causes
877 Acquired Immune Deficiency Syndrome (AIDS).

878 EPIVIR tablets and oral solution (used to treat HIV-1 infection) contain a higher dose of the
879 same active ingredient (lamivudine) than is in the medicine EPIVIR-HBV tablets and oral
880 solution (used to treat HBV). If you have both HIV-1 and HBV, you should not use EPIVIR-HBV
881 to treat your infections.

882 It is not known if EPIVIR is safe and effective in children under 3 months of age.

883 **When used with other antiretroviral medicines to treat HIV-1 infection, EPIVIR may help:**

- 884 • reduce the amount of HIV-1 in your blood. This is called “viral load”.
- 885 • increase the number of CD4+ (T) cells in your blood, which help fight off other infections.

886 Reducing the amount of HIV-1 and increasing the CD4+ (T) cells in your blood may help
887 improve your immune system. This may reduce your risk of death or getting infections that can
888 happen when your immune system is weak (opportunistic infections).

889 **EPIVIR does not cure HIV-1 infection or AIDS.** You must keep taking HIV-1 medicines to
890 control HIV-1 infection and decrease HIV-related illnesses.

891 **Avoid doing things that can spread HIV-1 infection to others:**

- 892 • Do not share or re-use needles or other injection equipment.
- 893 • Do not share personal items that can have blood or body fluids on them, like toothbrushes
894 and razor blades.
- 895 • Do not have any kind of sex without protection. Always practice safer sex by using a latex or
896 polyurethane condom to lower the chance of sexual contact with any body fluids such as
897 semen, vaginal secretions, or blood.

898 Ask your healthcare provider if you have any questions about how to prevent passing HIV to
899 other people.

900 **Who should not take EPIVIR?**

901 **Do not take EPIVIR** if you are allergic to lamivudine or any of the ingredients in EPIVIR. **See**
902 **“What are the ingredients in EPIVIR?”**.

903 **Do not take EPIVIR if you also take:**

- 904 • other medicines that contain lamivudine (COMBIVIR[®], EPIVIR-HBV[®], EPZICOM[®],

- 905 TRIZIVIR[®], TRIUMEQ[®])
906 • medicines that contain emtricitabine (ATRIPLA[®], COMPLERA[®], EMTRIVA[®], STRIBILD[®],
907 TRUVADA[®])

908 **What should I tell my healthcare provider before taking EPIVIR?**

909 **Before you take EPIVIR, tell your healthcare provider if you:**

- 910 • have or had liver problems, including hepatitis B or C infection.
911 • have kidney problems.
912 • have diabetes. Each 15-mL dose (150 mg) of EPIVIR oral solution contains 3 grams of
913 sucrose.
914 • have any other medical condition.
915 • are pregnant or plan to become pregnant. Taking EPIVIR during pregnancy has not been
916 associated with an increased risk of birth defects. Tell your healthcare provider if you
917 become pregnant while taking EPIVIR.

918 **Pregnancy Registry.** There is a pregnancy registry for women who take antiretroviral
919 medicines during pregnancy. The purpose of this registry is to collect information about the
920 health of you and your baby. Talk to your healthcare provider about how you can take part in
921 this registry.

- 922 • are breastfeeding or plan to breastfeed. **Do not breastfeed if you take EPIVIR.**
923 • You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to
924 your baby.
925 • Talk to your healthcare provider about the best way to feed your baby.

926 **Tell your healthcare provider about all the medicines you take**, including prescription and
927 over-the-counter medicines, vitamins, and herbal supplements. **Keep a list of your medicines**
928 **to show your healthcare provider and pharmacist. Do not start taking a new medicine**
929 **without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to
930 take EPIVIR with other medicines.

931 **How should I take EPIVIR?**

- 932 • Take EPIVIR exactly as your healthcare provider tells you.
933 • Do not change your dose or stop taking EPIVIR without talking with your healthcare
934 provider.
935 • For children 3 months and older, your healthcare provider will prescribe a dose of EPIVIR
936 based on your child's body weight.
937 • Take EPIVIR by mouth, with or without food.
938 • Tell your healthcare provider if you have trouble swallowing tablets. EPIVIR also comes as a
939 liquid (oral solution).
940 • Do not skip doses. If you miss a dose of EPIVIR, take it as soon as you remember. Do not
941 take 2 doses at the same time. If you are not sure about your dosing, call your healthcare

942 provider.
943 • If you take too much EPIVIR, call your healthcare provider or go to the nearest hospital
944 emergency room right away. It is important to stay under your healthcare provider's care
945 while taking EPIVIR.

946 **What are the possible side effects of EPIVIR?**

947 **EPIVIR can cause serious side effects. See “What is the most important information I**
948 **should know about EPIVIR?”.**

- 949 • **Use with interferon and ribavirin-based treatment.** Worsening of liver disease that has
950 sometimes led to death has happened in people infected with both HIV-1 and hepatitis C
951 virus who are taking antiretroviral medicines, and are also being treated for hepatitis C with
952 interferon with or without ribavirin. If you are taking EPIVIR and interferon with or without
953 ribavirin, tell your healthcare provider if you have any new symptoms.
- 954 • **Risk of inflammation of the pancreas (pancreatitis).** Children may be at risk for developing
955 pancreatitis during treatment with EPIVIR if they:
 - have taken nucleoside analogue medicines in the past
 - have a history of pancreatitis
 - have other risk factors for pancreatitis

956 **Call your healthcare provider right away if your child develops signs and symptoms of**
957 **pancreatitis including severe upper stomach-area pain, with or without nausea and**
958 **vomiting.** Your healthcare provider may tell you to stop giving EPIVIR to your child if their
959 symptoms and blood test results show that your child may have pancreatitis.

- 960 • **Changes in your immune system (Immune Reconstitution Syndrome)** can happen
961 when you start taking HIV-1 medicines. Your immune system may get stronger and begin to
962 fight infections that have been hidden in your body for a long time. Tell your healthcare
963 provider right away if you start having new symptoms after starting your HIV-1 medicine.
- 964 • **Changes in body fat can happen in people who take HIV-1 medicines.** These changes
965 may include increased amount of fat in the upper back and neck (“buffalo hump”), breast,
966 and around the middle of your body (trunk). Loss of fat from the legs, arms, and face may
967 also happen. The exact cause and long-term health effects of these problems are not
968 known.

969 The most common side effects of EPIVIR in adults include:

- headache
- nausea
- generally not feeling well
- tiredness
- nasal signs and symptoms
- diarrhea
- cough

970 The most common side effects of EPIVIR in children include fever and cough.

971 Tell your healthcare provider if you have any side effect that bothers you or that does not go
972 away. These are not all the possible side effects of EPIVIR. For more information, ask your
973 healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You
974 may report side effects to FDA at 1-800-FDA-1088.

975 **How should I store EPIVIR?**

- 976 • Store EPIVIR tablets and oral solution at room temperature between 68°F to 77°F (20°C to
977 25°C).
- 978 • Keep bottles of EPIVIR oral solution tightly closed.

979 **Keep EPIVIR and all medicines out of the reach of children.**

980 **General information about the safe and effective use of EPIVIR.**

981 Medicines are sometimes prescribed for purposes other than those listed in a Patient
982 Information leaflet. Do not use EPIVIR for a condition for which it was not prescribed. Do not
983 give EPIVIR to other people, even if they have the same symptoms that you have. It may harm
984 them.

985 If you would like more information, talk with your healthcare provider. You can ask your
986 pharmacist or healthcare provider for information about EPIVIR that is written for health
987 professionals.

988 For more information, go to www.viivhealthcare.com or call 1-877-844-8872.

989 **What are the ingredients in EPIVIR?**

990 **Active ingredient:** lamivudine

991 **Inactive ingredients:**

992 **EPIVIR scored 150-mg film-coated tablets:** hypromellose, magnesium stearate,
993 microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, and
994 titanium dioxide.

995 **EPIVIR 300-mg film-coated tablets:** black iron oxide, hypromellose, magnesium stearate,
996 microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, and
997 titanium dioxide.

998 **EPIVIR oral solution:** artificial strawberry and banana flavors, citric acid (anhydrous),
999 methylparaben, propylene glycol, propylparaben, sodium citrate (dihydrate), and sucrose
1000 (200 mg per mL).

1001 This Patient Information has been approved by the U.S. Food and Drug Administration.

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1003 Healthcare group of companies. EPIVIR-HBV is a registered trademark of the GSK group of
1004 companies.

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1008

Manufactured for:



ViiV Healthcare

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