

COMBIVIR[®]
(lamivudine/zidovudine)
Tablets

WARNING

ZIDOVUDINE, ONE OF THE TWO ACTIVE INGREDIENTS IN COMBIVIR, HAS BEEN ASSOCIATED WITH HEMATOLOGIC TOXICITY INCLUDING NEUTROPENIA AND SEVERE ANEMIA, PARTICULARLY IN PATIENTS WITH ADVANCED HUMAN IMMUNODEFICIENCY VIRUS (HIV) DISEASE (SEE WARNINGS). PROLONGED USE OF ZIDOVUDINE HAS BEEN ASSOCIATED WITH SYMPTOMATIC MYOPATHY.

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

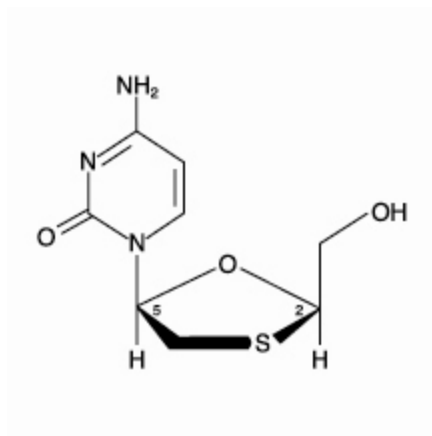
SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO ARE CO-INFECTED WITH HEPATITIS B VIRUS (HBV) AND HIV AND HAVE DISCONTINUED LAMIVUDINE, WHICH IS ONE COMPONENT OF COMBIVIR. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE COMBIVIR AND ARE CO-INFECTED WITH HIV AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS).

DESCRIPTION

COMBIVIR: COMBIVIR Tablets are combination tablets containing lamivudine and zidovudine. Lamivudine (EPIVIR[®], 3TC[®]) and zidovudine (RETROVIR[®], azidothymidine, AZT, or ZDV) are synthetic nucleoside analogues with activity against HIV.

COMBIVIR Tablets are for oral administration. Each film-coated tablet contains 150 mg of lamivudine, 300 mg of zidovudine, and the inactive ingredients colloidal silicon dioxide, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide.

Lamivudine: The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)-enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2',3'-dideoxy, 3'-thiacytidine. It has a molecular formula of C₈H₁₁N₃O₃S and a molecular weight of 229.3. It has the following structural formula:



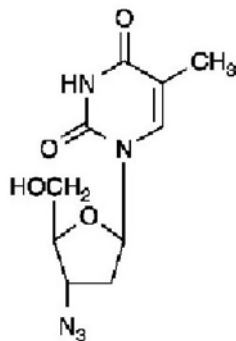
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41 Lamivudine is a white to off-white crystalline solid with a solubility of approximately
42 70 mg/mL in water at 20°C.

43 **Zidovudine:** The chemical name of zidovudine is 3'-azido-3'-deoxythymidine. It has a
44 molecular formula of C₁₀H₁₃N₅O₄ and a molecular weight of 267.24. It has the following
45 structural formula:

46



47

48 Zidovudine is a white to beige, odorless, crystalline solid with a solubility of 20.1 mg/mL in
49 water at 25°C.

50 MICROBIOLOGY

51 **Mechanism of Action: Lamivudine:** Lamivudine is a synthetic nucleoside analogue.
52 Intracellularly, lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine
53 triphosphate (3TC-TP). The principal mode of action of 3TC-TP is inhibition of reverse
54 transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue.
55 3TC-TP is a weak inhibitor of cellular DNA polymerases α , β , and γ .

56 **Zidovudine:** Zidovudine is a synthetic nucleoside analogue. Intracellularly, zidovudine is
57 phosphorylated to its active 5'-triphosphate metabolite, zidovudine triphosphate (ZDV-TP). The
58 principal mode of action of ZDV-TP is inhibition of RT via DNA chain termination after
59 incorporation of the nucleotide analogue. ZDV-TP is a weak inhibitor of the cellular DNA
60 polymerases α and γ and has been reported to be incorporated into the DNA of cells in culture.

61 **Antiviral Activity: Lamivudine Plus Zidovudine:** In HIV-1–infected MT-4 cells,
62 lamivudine in combination with zidovudine at various ratios exhibited synergistic antiretroviral
63 activity.

64 **Lamivudine:** The in vitro activity of lamivudine against HIV-1 was assessed in a number of
65 cell lines (including monocytes and fresh human peripheral blood lymphocytes) using standard
66 susceptibility assays. IC₅₀ values (50% inhibitory concentrations) were in the range of 0.003 to
67 15 μM (1 μM = 0.23 mcg/mL). The IC₅₀ values of lamivudine against different HIV-1 clades (A-
68 G) ranged from 0.001 to 0.120 μM, and against HIV-2 isolates from 0.003 to 0.120 μM.
69 Ribavirin (50 μM) decreased the anti-HIV-1 activity of lamivudine by 3.5 fold.

70 **Zidovudine:** In vitro activity of zidovudine against HIV-1 was assessed in a number of cell
71 lines (including monocytes and fresh human peripheral blood lymphocytes). The IC₅₀ and IC₉₀
72 values for zidovudine were 0.01 to 0.49 μM (1 μM = 0.27 mcg/mL) and 0.1 to 9 μM,
73 respectively. Zidovudine had anti–HIV-1 activity in all acute virus-cell infections tested.
74 However, zidovudine activity was substantially less in chronically infected cell lines. The IC₅₀
75 values of zidovudine against different HIV-1 clades (A-G) ranged from 0.00018 to 0.02 μM, and
76 against HIV-2 isolates from 0.00049 to 0.004 μM. In cell culture drug combination studies,
77 zidovudine demonstrates synergistic activity with the nucleoside reverse transcriptase inhibitors
78 (NRTIs) abacavir, didanosine, lamivudine, and zalcitabine; the non-nucleoside reverse
79 transcriptase inhibitors (NNRTIs) delavirdine and nevirapine; and the protease inhibitors (PIs)
80 indinavir, nelfinavir, ritonavir, and saquinavir; and additive activity with interferon alfa.
81 Ribavirin has been found to inhibit the phosphorylation of zidovudine in vitro.

82 **Resistance: Lamivudine Plus Zidovudine Administered As Separate**

83 **Formulations:** In patients receiving lamivudine monotherapy or combination therapy with
84 lamivudine plus zidovudine, HIV-1 isolates from most patients became phenotypically and
85 genotypically resistant to lamivudine within 12 weeks. In some patients harboring
86 zidovudine-resistant virus at baseline, phenotypic sensitivity to zidovudine was restored by
87 12 weeks of treatment with lamivudine and zidovudine. Combination therapy with lamivudine
88 plus zidovudine delayed the emergence of mutations conferring resistance to zidovudine.

89 HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from patients
90 after prolonged lamivudine/zidovudine therapy. Dual resistance required the presence of multiple
91 mutations, the most essential of which may be at codon 333 (Gly→Glu). The incidence of dual
92 resistance and the duration of combination therapy required before dual resistance occurs are
93 unknown.

94 **Lamivudine:** Lamivudine-resistant isolates of HIV-1 have been selected in vitro and have
95 also been recovered from patients treated with lamivudine or lamivudine plus zidovudine.
96 Genotypic analysis of isolates selected in vitro and recovered from lamivudine-treated patients
97 showed that the resistance was due to a specific amino acid substitution in the HIV-1 reverse
98 transcriptase at codon 184 changing the methionine to either isoleucine or valine.

99 **Zidovudine:** HIV isolates with reduced susceptibility to zidovudine have been selected
100 in vitro and were also recovered from patients treated with zidovudine. Genotypic analyses of the

101 isolates selected in vitro and recovered from zidovudine-treated patients showed mutations in the
102 HIV-1 RT gene resulting in 6 amino acid substitutions (M41L, D67N, K70R, L210W, T215Y or
103 F, and K219Q) that confer zidovudine resistance. In general, higher levels of resistance were
104 associated with greater number of mutations.

105 **Cross-Resistance:** Cross-resistance has been observed among NRTIs.

106 **Lamivudine Plus Zidovudine:** Cross-resistance between lamivudine and zidovudine has
107 not been reported. In some patients treated with lamivudine alone or in combination with
108 zidovudine, isolates have emerged with a mutation at codon 184, which confers resistance to
109 lamivudine. Cross-resistance to abacavir, didanosine, tenofovir, and zalcitabine has been
110 observed in some patients harboring lamivudine-resistant HIV-1 isolates. In some patients
111 treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple drugs,
112 including lamivudine, have emerged (see under Zidovudine below).

113 **Lamivudine:** See Lamivudine Plus Zidovudine (above).

114 **Zidovudine:** In a study of 167 HIV-infected patients, isolates (n = 2) with multi-drug
115 resistance to didanosine, lamivudine, stavudine, zalcitabine, and zidovudine were recovered from
116 patients treated for ≥ 1 year with zidovudine plus didanosine or zidovudine plus zalcitabine. The
117 pattern of resistance-associated mutations with such combination therapies was different (A62V,
118 V75I, F77L, F116Y, Q151M) from the pattern with zidovudine monotherapy, with the
119 Q151M mutation being most commonly associated with multi-drug resistance. The mutation at
120 codon 151 in combination with mutations at 62, 75, 77, and 116 results in a virus with reduced
121 susceptibility to didanosine, lamivudine, stavudine, zalcitabine, and zidovudine. Thymidine
122 analogue mutations (TAMs) are selected by zidovudine and confer cross-resistance to abacavir,
123 didanosine, stavudine, tenofovir, and zalcitabine.

124 **CLINICAL PHARMACOLOGY**

125 **Pharmacokinetics in Adults: COMBIVIR:** One COMBIVIR Tablet was bioequivalent to 1
126 EPIVIR Tablet (150 mg) plus 1 RETROVIR Tablet (300 mg) following single-dose
127 administration to fasting healthy subjects (n = 24).

128 **Lamivudine:** The pharmacokinetic properties of lamivudine in fasting patients are
129 summarized in Table 1. Following oral administration, lamivudine is rapidly absorbed and
130 extensively distributed. Binding to plasma protein is low. Approximately 70% of an intravenous
131 dose of lamivudine is recovered as unchanged drug in the urine. Metabolism of lamivudine is a
132 minor route of elimination. In humans, the only known metabolite is the trans-sulfoxide
133 metabolite (approximately 5% of an oral dose after 12 hours).

134 **Zidovudine:** The pharmacokinetic properties of zidovudine in fasting patients are
135 summarized in Table 1. Following oral administration, zidovudine is rapidly absorbed and
136 extensively distributed. Binding to plasma protein is low. Zidovudine is eliminated primarily by
137 hepatic metabolism. The major metabolite of zidovudine is 3'-azido-3'-deoxy-5'-O- β -D-
138 glucopyranuronosylthymidine (GZDV). GZDV area under the curve (AUC) is about 3-fold
139 greater than the zidovudine AUC. Urinary recovery of zidovudine and GZDV accounts for 14%

140 and 74% of the dose following oral administration, respectively. A second metabolite, 3'-amino-
 141 3'-deoxythymidine (AMT), has been identified in plasma. The AMT AUC was one fifth of the
 142 zidovudine AUC.

143

144 **Table 1. Pharmacokinetic Parameters* for Lamivudine and Zidovudine in Adults**

Parameter	Lamivudine		Zidovudine	
Oral bioavailability (%)	86 ± 16	n = 12	64 ± 10	n = 5
Apparent volume of distribution (L/kg)	1.3 ± 0.4	n = 20	1.6 ± 0.6	n = 8
Plasma protein binding (%)	<36		<38	
CSF:plasma ratio [†]	0.12 [0.04 to 0.47]	n = 38 [‡]	0.60 [0.04 to 2.62]	n = 39 [§]
Systemic clearance (L/hr/kg)	0.33 ± 0.06	n = 20	1.6 ± 0.6	n = 6
Renal clearance (L/hr/kg)	0.22 ± 0.06	n = 20	0.34 ± 0.05	n = 9
Elimination half-life (hr)	5 to 7		0.5 to 3	

145 *Data presented as mean ± standard deviation except where noted.

146 [†]Median [range].

147 [‡]Children.

148 [§]Adults.

149 ^{||}Approximate range.

150

151 **Effect of Food on Absorption of COMBIVIR:** COMBIVIR may be administered with or
 152 without food. The extent of lamivudine and zidovudine absorption (AUC) following
 153 administration of COMBIVIR with food was similar when compared to fasting healthy subjects
 154 (n = 24).

155 **Special Populations: Impaired Renal Function: COMBIVIR:** Because lamivudine and
 156 zidovudine require dose adjustment in the presence of renal insufficiency, COMBIVIR is not
 157 recommended for patients with impaired renal function (creatinine clearance <50 mL/min) (see
 158 PRECAUTIONS).

159 **Impaired Hepatic Function: COMBIVIR:** A reduction in the daily dose of zidovudine
 160 may be necessary in patients with mild to moderate impaired hepatic function or liver cirrhosis.
 161 Because COMBIVIR is a fixed-dose combination that cannot be adjusted for this patient
 162 population, COMBIVIR is not recommended for patients with impaired hepatic function.

163 **Pregnancy:** See PRECAUTIONS: Pregnancy.

164 **COMBIVIR:** No data are available.

165 **Zidovudine:** Zidovudine pharmacokinetics has been studied in a Phase 1 study of
 166 8 women during the last trimester of pregnancy. As pregnancy progressed, there was no evidence
 167 of drug accumulation. The pharmacokinetics of zidovudine was similar to that of nonpregnant
 168 adults. Consistent with passive transmission of the drug across the placenta, zidovudine
 169 concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at
 170 delivery. Although data are limited, methadone maintenance therapy in 5 pregnant women did

171 not appear to alter zidovudine pharmacokinetics. In a nonpregnant adult population, a potential
172 for interaction has been identified (see CLINICAL PHARMACOLOGY: Drug Interactions).

173 **Nursing Mothers:** See PRECAUTIONS: Nursing Mothers.

174 **COMBIVIR:** No data are available.

175 **Lamivudine:** Samples of breast milk obtained from 20 mothers receiving lamivudine
176 monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice daily and
177 300 mg zidovudine twice daily) had measurable concentrations of lamivudine.

178 **Zidovudine:** After administration of a single dose of 200 mg zidovudine to
179 13 HIV-infected women, the mean concentration of zidovudine was similar in human milk and
180 serum.

181 **Pediatric Patients: COMBIVIR:** COMBIVIR should not be administered to pediatric
182 patients less than 12 years of age because it is a fixed-dose combination that cannot be adjusted
183 for this patient population.

184 **Geriatric Patients:** The pharmacokinetics of lamivudine and zidovudine have not been
185 studied in patients over 65 years of age.

186 **Gender: COMBIVIR:** A pharmacokinetic study in healthy male (n = 12) and female (n = 12)
187 subjects showed no gender differences in zidovudine exposure (AUC_{∞}) or lamivudine AUC_{∞}
188 normalized for body weight.

189 **Race: Lamivudine:** There are no significant racial differences in lamivudine
190 pharmacokinetics.

191 **Zidovudine:** The pharmacokinetics of zidovudine with respect to race have not been
192 determined.

193 **Drug Interactions:** See PRECAUTIONS: Drug Interactions.

194 **COMBIVIR:** No drug interaction studies have been conducted using COMBIVIR Tablets.

195 **Lamivudine Plus Zidovudine:** No clinically significant alterations in lamivudine or
196 zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-infected adult patients
197 given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine
198 (300 mg q 12 hr).

199

200 **Table 2. Effect of Coadministered Drugs on Lamivudine and Zidovudine AUC***
 201 **Note: ROUTINE DOSE MODIFICATION OF LAMIVUDINE AND ZIDOVUDINE IS**
 202 **NOT WARRANTED WITH COADMINISTRATION OF THE FOLLOWING**
 203 **DRUGS.**

Drugs That May Alter Lamivudine Blood Concentrations					
Coadministered Drug and Dose	Lamivudine Dose	n	Lamivudine Concentrations		Concentration of Coadministered Drug
			AUC	Variability	
Nelfinavir 750 mg q 8 hr x 7 to 10 days	single 150 mg	11	↑AUC 10%	95% CI: 1% to 20%	↔
Trimethoprim 160 mg/ Sulfamethoxazole 800 mg daily x 5 days	single 300 mg	14	↑AUC 43%	90% CI: 32% to 55%	↔
Drugs That May Alter Zidovudine Blood Concentrations					
Coadministered Drug and Dose	Zidovudine Dose	n	Zidovudine Concentrations		Concentration of Coadministered Drug
			AUC	Variability	
Atovaquone 750 mg q 12 hr with food	200 mg q 8 hr	14	↑AUC 31%	Range 23% to 78% [†]	↔
Fluconazole 400 mg daily	200 mg q 8 hr	12	↑AUC 74%	95% CI: 54% to 98%	Not Reported
Methadone 30 to 90 mg daily	200 mg q 4 hr	9	↑AUC 43%	Range 16% to 64% [†]	↔
Nelfinavir 750 mg q 8 hr x 7 to 10 days	single 200 mg	11	↓AUC 35%	Range 28% to 41%	↔
Probenecid 500 mg q 6 hr x 2 days	2 mg/kg q 8 hr x 3 days	3	↑AUC 106%	Range 100% to 170% [†]	Not Assessed
Ritonavir 300 mg q 6 hr x 4 days	200 mg q 8 hr x 4 days	9	↓AUC 25%	95% CI: 15% to 34%	↔
Valproic acid 250 mg or 500 mg q 8 hr x 4 days	100 mg q 8 hr x 4 days	6	↑AUC 80%	Range 64% to 130% [†]	Not Assessed

204 ↑ = Increase; ↓ = Decrease; ↔ = no significant change; AUC = area under the concentration
 205 versus time curve; CI = confidence interval.

206 *This table is not all inclusive.
207 †Estimated range of percent difference.

208
209 **Ribavirin:** In vitro data indicate ribavirin reduces phosphorylation of lamivudine, stavudine,
210 and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular
211 triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV/HCV
212 virologic suppression) interaction was observed when ribavirin and lamivudine (n = 18),
213 stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug regimen to
214 HIV/HCV co-infected patients (see WARNINGS).

215 INDICATIONS AND USAGE

216 **COMBIVIR is indicated in combination with other antiretrovirals for the treatment of**
217 **HIV-1 infection.**

218 **Description of Clinical Studies: COMBIVIR:** There have been no clinical trials conducted
219 with COMBIVIR. See CLINICAL PHARMACOLOGY for information about bioequivalence.
220 One COMBIVIR Tablet given twice daily is an alternative regimen to EPIVIR Tablets 150 mg
221 twice daily plus RETROVIR 600 mg per day in divided doses.

222 **Lamivudine Plus Zidovudine:** The NUCB3007 (CAESAR) study was conducted using
223 EPIVIR 150-mg Tablets (150 mg twice daily) and RETROVIR 100-mg Capsules (2 x 100 mg 3
224 times daily). CAESAR was a multi-center, double-blind, placebo-controlled study comparing
225 continued current therapy [zidovudine alone (62% of patients) or zidovudine with didanosine or
226 zalcitabine (38% of patients)] to the addition of EPIVIR or EPIVIR plus an investigational non-
227 nucleoside reverse transcriptase inhibitor, randomized 1:2:1. A total of 1,816 HIV-infected adults
228 with 25 to 250 (median 122) CD4 cells/mm³ at baseline were enrolled: median age was 36 years,
229 87% were male, 84% were nucleoside-experienced, and 16% were therapy-naive. The median
230 duration on study was 12 months. Results are summarized in Table 3.

231
232 **Table 3. Number of Patients (%) With At Least 1 HIV Disease-Progression Event or Death**

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

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

235 CONTRAINDICATIONS

236 COMBIVIR Tablets are contraindicated in patients with previously demonstrated clinically
237 significant hypersensitivity to any of the components of the product.

238 **WARNINGS**

239 COMBIVIR is a fixed-dose combination of lamivudine and zidovudine. Ordinarily,
240 COMBIVIR should not be administered concomitantly with lamivudine, zidovudine,
241 EPZICOM™, a fixed-dose combination of abacavir and lamivudine, or TRIZIVIR®, a fixed-dose
242 combination of abacavir, lamivudine, and zidovudine.

243 The complete prescribing information for all agents being considered for use with
244 COMBIVIR should be consulted before combination therapy with COMBIVIR is initiated.

245 **Bone Marrow Suppression:** COMBIVIR should be used with caution in patients who have
246 bone marrow compromise evidenced by granulocyte count <1,000 cells/mm³ or hemoglobin
247 <9.5 g/dL (see ADVERSE REACTIONS).

248 Frequent blood counts are strongly recommended in patients with advanced HIV disease who
249 are treated with COMBIVIR. For HIV-infected individuals and patients with asymptomatic or
250 early HIV disease, periodic blood counts are recommended.

251 **Lactic Acidosis/Severe Hepatomegaly With Steatosis:** Lactic acidosis and severe
252 hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside
253 analogues alone or in combination, including lamivudine, zidovudine, and other antiretrovirals.
254 A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may
255 be risk factors. Particular caution should be exercised when administering COMBIVIR to any
256 patient with known risk factors for liver disease; however, cases have also been reported in
257 patients with no known risk factors. Treatment with COMBIVIR should be suspended in any
258 patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced
259 hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked
260 transaminase elevations).

261 **Myopathy:** Myopathy and myositis, with pathological changes similar to that produced by HIV
262 disease, have been associated with prolonged use of zidovudine, and therefore may occur with
263 therapy with COMBIVIR.

264 **Posttreatment Exacerbations of Hepatitis:** In clinical trials in non-HIV-infected patients
265 treated with lamivudine for chronic HBV, clinical and laboratory evidence of exacerbations of
266 hepatitis have occurred after discontinuation of lamivudine. These exacerbations have been
267 detected primarily by serum ALT elevations in addition to re-emergence of hepatitis B viral
268 DNA (HBV DNA). Although most events appear to have been self-limited, fatalities have been
269 reported in some cases. Similar events have been reported from post-marketing experience after
270 changes from lamivudine-containing HIV treatment regimens to non-lamivudine-containing
271 regimens in patients infected with both HIV and HBV. The causal relationship to discontinuation
272 of lamivudine treatment is unknown. Patients should be closely monitored with both clinical and
273 laboratory follow-up for at least several months after stopping treatment. There is insufficient
274 evidence to determine whether re-initiation of lamivudine alters the course of posttreatment
275 exacerbations of hepatitis.

276 **Use With Interferon- and Ribavirin-Based Regimens:** In vitro studies have shown
277 ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine
278 and zidovudine. Although no evidence of a pharmacokinetic or pharmacodynamic interaction
279 (e.g., loss of HIV/HCV virologic suppression) was seen when ribavirin was coadministered with
280 lamivudine or zidovudine in HIV/HCV co-infected patients (see CLINICAL
281 PHARMACOLOGY: Drug Interactions), **hepatic decompensation (some fatal) has occurred**
282 **in HIV/HCV co-infected patients receiving combination antiretroviral therapy for HIV and**
283 **interferon alfa with or without ribavirin.** Patients receiving interferon alfa with or without
284 ribavirin and COMBIVIR should be closely monitored for treatment-associated toxicities,
285 especially hepatic decompensation, neutropenia, and anemia. Discontinuation of COMBIVIR
286 should be considered as medically appropriate. Dose reduction or discontinuation of interferon
287 alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed,
288 including hepatic decompensation (e.g., Childs Pugh >6) (see the complete prescribing
289 information for interferon and ribavirin).

290 **PRECAUTIONS**

291 **Patients With HIV and Hepatitis B Virus Co-infection:** Safety and efficacy of lamivudine
292 have not been established for treatment of chronic hepatitis B in patients dually infected with
293 HIV and HBV. In non-HIV-infected patients treated with lamivudine for chronic hepatitis B,
294 emergence of lamivudine-resistant HBV has been detected and has been associated with
295 diminished treatment response (see EPIVIR-HBV package insert for additional information).
296 Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been
297 reported in HIV-infected patients who have received lamivudine-containing antiretroviral
298 regimens in the presence of concurrent infection with hepatitis B virus. Posttreatment
299 exacerbations of hepatitis have also been reported (see WARNINGS).

300 **Patients With Impaired Renal Function:** Reduction of the dosages of lamivudine and
301 zidovudine is recommended for patients with impaired renal function. Patients with creatinine
302 clearance <50 mL/min should not receive COMBIVIR.

303 **Patients With Impaired Hepatic Function:** A reduction in the daily dose of zidovudine
304 may be necessary in patients with mild to moderate impaired hepatic function or liver cirrhosis.
305 COMBIVIR is not recommended for patients with impaired hepatic function.

306 **Immune Reconstitution Syndrome:** Immune reconstitution syndrome has been reported in
307 patients treated with combination antiretroviral therapy, including COMBIVIR. During the initial
308 phase of combination antiretroviral treatment, patients whose immune system responds may
309 develop an inflammatory response to indolent or residual opportunistic infections (such as
310 *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or
311 tuberculosis), which may necessitate further evaluation and treatment.

312 **Fat Redistribution:** Redistribution/accumulation of body fat including central obesity,
313 dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast
314 enlargement, and “cushingoid appearance” have been observed in patients receiving

315 antiretroviral therapy. The mechanism and long-term consequences of these events are currently
316 unknown. A causal relationship has not been established.

317 **Information for Patients:** COMBIVIR is not a cure for HIV infection and patients may
318 continue to experience illnesses associated with HIV infection, including opportunistic
319 infections. Patients should be advised that the use of COMBIVIR has not been shown to reduce
320 the risk of transmission of HIV to others through sexual contact or blood contamination. **Patients**
321 **should be advised of the importance of taking COMBIVIR exactly as it is prescribed.**

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

325 **Lamivudine:** Patients co-infected with HIV and HBV should be informed that deterioration
326 of liver disease has occurred in some cases when treatment with lamivudine was discontinued.
327 Patients should be advised to discuss any changes in regimen with their physician.

328 **Zidovudine:** Patients should be informed that the important toxicities associated with
329 zidovudine are neutropenia and/or anemia. They should be told of the extreme importance of
330 having their blood counts followed closely while on therapy, especially for patients with
331 advanced HIV disease.

332 **Drug Interactions: Lamivudine:** Trimethoprim (TMP) 160 mg/sulfamethoxazole (SMX)
333 800 mg once daily has been shown to increase lamivudine exposure (AUC). The effect of higher
334 doses of TMP/SMX on lamivudine pharmacokinetics has not been investigated (see CLINICAL
335 PHARMACOLOGY). No data are available regarding the potential for interactions with other
336 drugs that have renal clearance mechanisms similar to that of lamivudine.

337 Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another.
338 Therefore, use of COMBIVIR in combination with zalcitabine is not recommended.

339 **Zidovudine:** Coadministration of ganciclovir, interferon alfa, and other bone marrow
340 suppressive or cytotoxic agents may increase the hematologic toxicity of zidovudine.

341 Concomitant use of COMBIVIR with stavudine should be avoided since an antagonistic
342 relationship with zidovudine has been demonstrated in vitro. In addition, concomitant use of
343 COMBIVIR with doxorubicin or ribavirin should be avoided because an antagonistic
344 relationship with zidovudine has been demonstrated in vitro.

345 See CLINICAL PHARMACOLOGY for additional drug interactions.

346 **Carcinogenesis, Mutagenesis, and Impairment of Fertility: Carcinogenicity:**

347 **Lamivudine:** Long-term carcinogenicity studies with lamivudine in mice and rats showed
348 no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats)
349 those observed in humans at the recommended therapeutic dose for HIV infection.

350 **Zidovudine:** Zidovudine was administered orally at 3 dosage levels to separate groups of
351 mice and rats (60 females and 60 males in each group). Initial single daily doses were 30, 60, and
352 120 mg/kg/day in mice and 80, 220, and 600 mg/kg/day in rats. The doses in mice were reduced
353 to 20, 30, and 40 mg/kg/day after day 90 because of treatment-related anemia, whereas in rats

354 only the high dose was reduced to 450 mg/kg/day on day 91 and then to 300 mg/kg/day on
355 day 279.

356 In mice, 7 late-appearing (after 19 months) vaginal neoplasms (5 nonmetastasizing squamous
357 cell carcinomas, 1 squamous cell papilloma, and 1 squamous polyp) occurred in animals given
358 the highest dose. One late-appearing squamous cell papilloma occurred in the vagina of a
359 middle-dose animal. No vaginal tumors were found at the lowest dose.

360 In rats, 2 late-appearing (after 20 months), nonmetastasizing vaginal squamous cell
361 carcinomas occurred in animals given the highest dose. No vaginal tumors occurred at the low or
362 middle dose in rats. No other drug-related tumors were observed in either sex of either species.

363 At doses that produced tumors in mice and rats, the estimated drug exposure (as measured by
364 AUC) was approximately 3 times (mouse) and 24 times (rat) the estimated human exposure at
365 the recommended therapeutic dose of 100 mg every 4 hours.

366 Two transplacental carcinogenicity studies were conducted in mice. One study administered
367 zidovudine at doses of 20 mg/kg/day or 40 mg/kg/day from gestation day 10 through parturition
368 and lactation with dosing continuing in offspring for 24 months postnatally. The doses of
369 zidovudine employed in this study produced zidovudine exposures approximately 3 times the
370 estimated human exposure at recommended doses. After 24 months at the highest dose, an
371 increase in incidence of vaginal tumors was noted with no increase in tumors in the liver or lung
372 or any other organ in either gender. These findings are consistent with results of the standard oral
373 carcinogenicity study in mice, as described earlier. A second study administered zidovudine at
374 maximum tolerated doses of 12.5 mg/day or 25 mg/day (~1,000 mg/kg nonpregnant body weight
375 or ~450 mg/kg of term body weight) to pregnant mice from days 12 through 18 of gestation.
376 There was an increase in the number of tumors in the lung, liver, and female reproductive tracts
377 in the offspring of mice receiving the higher dose level of zidovudine.

378 It is not known how predictive the results of rodent carcinogenicity studies may be for
379 humans.

380 **Mutagenicity: Lamivudine:** Lamivudine was mutagenic in an L5178Y/TK^{+/-} mouse
381 lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes.
382 Lamivudine was negative in a microbial mutagenicity assay, in an in vitro cell transformation
383 assay, in a rat micronucleus test, in a rat bone marrow cytogenetic assay, and in an assay for
384 unscheduled DNA synthesis in rat liver.

385 **Zidovudine:** Zidovudine was mutagenic in an L5178Y/TK^{+/-} mouse lymphoma assay,
386 positive in an in vitro cell transformation assay, clastogenic in a cytogenetic assay using cultured
387 human lymphocytes, and positive in mouse and rat micronucleus tests after repeated doses. It
388 was negative in a cytogenetic study in rats given a single dose.

389 **Impairment of Fertility: Lamivudine:** In a study of reproductive performance,
390 lamivudine, administered to male and female rats at doses up to 130 times the usual adult dose
391 based on body surface area considerations, revealed no evidence of impaired fertility (judged by
392 conception rates) and no effect on the survival, growth, and development to weaning of the
393 offspring.

394 **Zidovudine:** Zidovudine, administered to male and female rats at doses up to 7 times the
395 usual adult dose based on body surface area considerations, had no effect on fertility judged by
396 conception rates.

397 **Pregnancy:** Pregnancy Category C.

398 **COMBIVIR:** There are no adequate and well-controlled studies of COMBIVIR in pregnant
399 women. Reproduction studies with lamivudine and zidovudine have been performed in animals
400 (see Lamivudine and Zidovudine sections below). COMBIVIR should be used during pregnancy
401 only if the potential benefits outweigh the risks.

402 **Lamivudine:** Studies in pregnant rats and rabbits showed that lamivudine is transferred to
403 the fetus through the placenta. Reproduction studies with orally administered lamivudine have
404 been performed in rats and rabbits at doses up to 4,000 mg/kg/day and 1,000 mg/kg/day,
405 respectively, producing plasma levels up to approximately 35 times that for the adult HIV dose.
406 No evidence of teratogenicity due to lamivudine was observed. Evidence of early
407 embryoletality was seen in the rabbit at exposure levels similar to those observed in humans,
408 but there was no indication of this effect in the rat at exposure levels up to 35 times those in
409 humans.

410 **Zidovudine:** Reproduction studies with orally administered zidovudine in the rat and in the
411 rabbit at doses up to 500 mg/kg/day revealed no evidence of teratogenicity with zidovudine.
412 Zidovudine treatment resulted in embryo/fetal toxicity as evidenced by an increase in the
413 incidence of fetal resorptions in rats given 150 or 450 mg/kg/day and rabbits given
414 500 mg/kg/day. The doses used in the teratology studies resulted in peak zidovudine plasma
415 concentrations (after one half of the daily dose) in rats 66 to 226 times, and in rabbits 12 to
416 87 times, mean steady-state peak human plasma concentrations (after one sixth of the daily dose)
417 achieved with the recommended daily dose (100 mg every 4 hours). In an additional teratology
418 study in rats, a dose of 3,000 mg/kg/day (very near the oral median lethal dose in rats of
419 3,683 mg/kg) caused marked maternal toxicity and an increase in the incidence of fetal
420 malformations. This dose resulted in peak zidovudine plasma concentrations 350 times peak
421 human plasma concentrations. No evidence of teratogenicity was seen in this experiment at doses
422 of 600 mg/kg/day or less. Two rodent carcinogenicity studies were conducted (see
423 Carcinogenesis, Mutagenesis, Impairment of Fertility).

424 **Antiretroviral Pregnancy Registry:** To monitor maternal-fetal outcomes of pregnant
425 women exposed to COMBIVIR and other antiretroviral agents, an Antiretroviral Pregnancy
426 Registry has been established. Physicians are encouraged to register patients by calling 1-800-
427 258-4263.

428 **Nursing Mothers: The Centers for Disease Control and Prevention recommend that**
429 **HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission**
430 **of HIV infection.** No specific studies of lamivudine and zidovudine excretion in breast milk
431 after dosing with COMBIVIR have been performed. Lamivudine and zidovudine are excreted in
432 human breast milk (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Nursing Mothers).

433 A study in lactating rats administered 45 mg/kg of lamivudine showed that lamivudine
434 concentrations in milk were slightly greater than those in plasma.

435 Because of both the potential for HIV transmission and the potential for serious adverse
436 reactions in nursing infants, **mothers should be instructed not to breastfeed if they are**
437 **receiving COMBIVIR.**

438 **Pediatric Use:** COMBIVIR should not be administered to pediatric patients less than 12 years
439 of age because it is a fixed-dose combination that cannot be adjusted for this patient population.

440 **Geriatric Use:** Clinical studies of COMBIVIR did not include sufficient numbers of subjects
441 aged 65 and over to determine whether they respond differently from younger subjects. In
442 general, dose selection for an elderly patient should be cautious, reflecting the greater frequency
443 of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug
444 therapy. COMBIVIR is not recommended for patients with impaired renal function (i.e.,
445 creatinine clearance <50 mL/min; see PRECAUTIONS: Patients with Impaired Renal Function
446 and DOSAGE AND ADMINISTRATION).

447 **ADVERSE REACTIONS**

448 **Lamivudine Plus Zidovudine Administered As Separate Formulations:** In
449 4 randomized, controlled trials of EPIVIR 300 mg per day plus RETROVIR 600 mg per day, the
450 following selected clinical and laboratory adverse events were observed (see Tables 4 and 5).
451

452 **Table 4. Selected Clinical Adverse Events (≥5% Frequency) in 4 Controlled Clinical Trials**
 453 **With EPIVIR 300 mg/day and RETROVIR 600 mg/day**

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

454
 455 Pancreatitis was observed in 3 of the 656 adult patients (<0.5%) who received EPIVIR in
 456 controlled clinical trials.

457 Selected laboratory abnormalities observed during therapy are listed in Table 5.

458

459 **Table 5. Frequencies of Selected Laboratory Abnormalities Among Adults in 4 Controlled**
 460 **Clinical Trials of EPIVIR 300 mg/day plus RETROVIR 600 mg/day***

Test (Abnormal Level)	EPIVIR plus RETROVIR % (n)
Neutropenia (ANC<750/mm ³)	7.2% (237)
Anemia (Hgb<8.0 g/dL)	2.9% (241)
Thrombocytopenia (platelets<50,000/mm ³)	0.4% (240)
ALT (>5.0 x ULN)	3.7% (241)
AST (>5.0 x ULN)	1.7% (241)
Bilirubin (>2.5 x ULN)	0.8% (241)
Amylase (>2.0 x ULN)	4.2% (72)

461 ULN = Upper limit of normal.

462 ANC = Absolute neutrophil count.

463 n = Number of patients assessed.

464 * Frequencies of these laboratory abnormalities were higher in patients with mild laboratory
 465 abnormalities at baseline.

466

467 **Observed During Clinical Practice:** In addition to adverse events reported from clinical
 468 trials, the following events have been identified during post-approval use of EPIVIR,
 469 RETROVIR, and/or COMBIVIR. Because they are reported voluntarily from a population of
 470 unknown size, estimates of frequency cannot be made. These events have been chosen for
 471 inclusion due to a combination of their seriousness, frequency of reporting, or potential causal
 472 connection to EPIVIR, RETROVIR, and/or COMBIVIR.

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

475 **Cardiovascular:** Cardiomyopathy.

476 **Endocrine and Metabolic:** Gynecomastia, hyperglycemia.

477 **Gastrointestinal:** Oral mucosal pigmentation, stomatitis.

478 **General:** Vasculitis, weakness.

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

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

483 **Hypersensitivity:** Sensitization reactions (including anaphylaxis), urticaria.

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

485 **Nervous:** Paresthesia, peripheral neuropathy, seizures.

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

487 **Skin:** Alopecia, erythema multiforme, Stevens-Johnson syndrome.

488 **OVERDOSAGE**

489 **COMBIVIR:** There is no known antidote for COMBIVIR.

490 **Lamivudine:** One case of an adult ingesting 6 grams of lamivudine was reported; there were no
491 clinical signs or symptoms noted and hematologic tests remained normal. Because a negligible
492 amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal
493 dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would
494 provide clinical benefit in a lamivudine overdose event.

495 **Zidovudine:** Acute overdoses of zidovudine have been reported in pediatric patients and adults.
496 These involved exposures up to 50 grams. The only consistent findings were nausea and
497 vomiting. Other reported occurrences included headache, dizziness, drowsiness, lethargy,
498 confusion, and 1 report of a grand mal seizure. Hematologic changes were transient. All patients
499 recovered. Hemodialysis and peritoneal dialysis appear to have a negligible effect on the removal
500 of zidovudine, while elimination of its primary metabolite, GZDV, is enhanced.

501 **DOSAGE AND ADMINISTRATION**

502 The recommended oral dose of COMBIVIR for adults and adolescents (at least 12 years of
503 age) is 1 tablet (containing 150 mg of lamivudine and 300 mg of zidovudine) twice daily.

504 **Dose Adjustment:** Because it is a fixed-dose combination, COMBIVIR should not be
505 prescribed for patients requiring dosage adjustment such as those with reduced renal function
506 (creatinine clearance <50 mL/min), patients with hepatic impairment, or patients experiencing
507 dose-limiting adverse events.

508 **HOW SUPPLIED**

509 COMBIVIR Tablets, containing 150 mg lamivudine and 300 mg zidovudine, are white,
510 film-coated, modified-capsule-shaped tablets engraved with “GXFC3” on one side. They are
511 available as follows:

512 60 Tablets/Bottle (NDC 0173-0595-00)

513 **Store between 2° and 30°C (36° and 86°F).**

514 Unit Dose Pack of 120 (NDC 0173-0595-02)

515 **Store between 2° and 30°C (36° and 86°F).**

516

517



518

519 GlaxoSmithKline

520 Research Triangle Park, NC 27709

521

522 Lamivudine is manufactured under agreement from

523 **Shire Pharmaceuticals Group plc**

524 Basingstoke, UK

525

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527

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