

TRIZIVIR[®]
(abacavir sulfate, lamivudine, and zidovudine)
Tablets

WARNINGS

TRIZIVIR contains 3 nucleoside analogues (abacavir sulfate, lamivudine, and zidovudine) and is intended only for patients whose regimen would otherwise include these 3 components.

Hypersensitivity Reactions: Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir sulfate, a component of TRIZIVIR. Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by a sign or symptom in 2 or more of the following groups: (1) fever, (2) rash, (3) gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain), (4) constitutional (including generalized malaise, fatigue, or achiness), and (5) respiratory (including dyspnea, cough, or pharyngitis).

Discontinue TRIZIVIR as soon as a hypersensitivity reaction is suspected.

Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. Prior to initiating therapy with abacavir, screening for the HLA-B*5701 allele is recommended; this approach has been found to decrease the risk of hypersensitivity reaction. Screening is also recommended prior to reinitiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. HLA-B*5701-negative patients may develop a suspected hypersensitivity reaction to abacavir; however, this occurs significantly less frequently than in HLA-B*5701-positive patients.

Regardless of HLA-B*5701 status, permanently discontinue TRIZIVIR if hypersensitivity cannot be ruled out, even when other diagnoses are possible.

Following a hypersensitivity reaction to abacavir, NEVER restart TRIZIVIR or any other abacavir-containing product because more severe symptoms can occur within hours and may include life-threatening hypotension and death.

Reintroduction of TRIZIVIR or any other abacavir-containing product, even in patients who have no identified history or unrecognized symptoms of hypersensitivity to abacavir therapy, can result in serious or fatal hypersensitivity reactions. Such reactions can occur within hours (see WARNINGS and PRECAUTIONS: Information for Patients).

Hematologic Toxicity: Zidovudine has been associated with hematologic toxicity including neutropenia and severe anemia, particularly in patients with advanced Human Immunodeficiency Virus (HIV-1) disease (see WARNINGS). Prolonged use of zidovudine has been associated with symptomatic myopathy.

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Lactic Acidosis and Severe Hepatomegaly: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including abacavir, lamivudine, zidovudine, and other antiretrovirals (see WARNINGS).

Exacerbations of Hepatitis B: Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and HIV-1 and have discontinued lamivudine, which is one component of TRIZIVIR. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue TRIZIVIR and are co-infected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted (see WARNINGS).

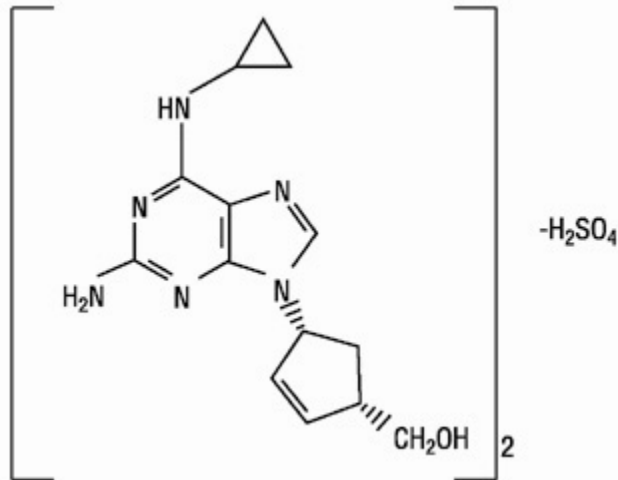
52 **DESCRIPTION**

53 **TRIZIVIR:** TRIZIVIR Tablets contain the following 3 synthetic nucleoside analogues: abacavir
54 sulfate (ZIAGEN[®]), lamivudine (also known as EPIVIR[®] or 3TC), and zidovudine (also known
55 as RETROVIR[®], azidothymidine, or ZDV) with inhibitory activity against HIV-1.

56 TRIZIVIR Tablets are for oral administration. Each film-coated tablet contains the active
57 ingredients 300 mg of abacavir as abacavir sulfate, 150 mg of lamivudine, and 300 mg of
58 zidovudine, and the inactive ingredients magnesium stearate, microcrystalline cellulose, and
59 sodium starch glycolate. The tablets are coated with a film (OPADRY[®] green 03B11434) that is
60 made of FD&C Blue No. 2, hypromellose, polyethylene glycol, titanium dioxide, and yellow
61 iron oxide.

62 **Abacavir Sulfate:** The chemical name of abacavir sulfate is (1*S*,*cis*)-4-[2-amino-6-
63 (cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1). Abacavir
64 sulfate is the enantiomer with *1S*, *4R* absolute configuration on the cyclopentene ring. It has a
65 molecular formula of (C₁₄H₁₈N₆O)₂•H₂SO₄ and a molecular weight of 670.76 daltons. It has the
66 following structural formula:

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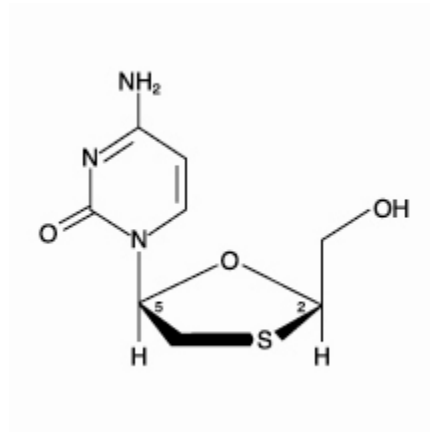
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70 Abacavir sulfate is a white to off-white solid with a solubility of approximately 77 mg/mL in
71 distilled water at 25°C.

72 In vivo, abacavir sulfate dissociates to its free base, abacavir. In this insert, all dosages for
73 ZIAGEN (abacavir sulfate) are expressed in terms of abacavir.

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

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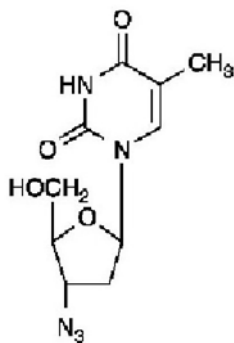


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82 Lamivudine is a white to off-white crystalline solid with a solubility of approximately
83 70 mg/mL in water at 20°C.

84 **Zidovudine:** The chemical name of zidovudine is 3'-azido-3'-deoxythymidine. It has a
85 molecular formula of C₁₀H₁₃N₅O₄ and a molecular weight of 267.24 daltons. It has the following
86 structural formula:

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90 Zidovudine is a white to beige, crystalline solid with a solubility of 20.1 mg/mL in water at
91 25°C.

92 MICROBIOLOGY

93 Mechanism of Action:

94 **Abacavir:** Abacavir is a carbocyclic synthetic nucleoside analogue. Abacavir is converted by
95 cellular enzymes to the active metabolite, carbovir triphosphate (CBV-TP), an analogue of
96 deoxyguanosine-5'-triphosphate (dGTP). CBV-TP inhibits the activity of HIV-1 reverse
97 transcriptase (RT) both by competing with the natural substrate dGTP and by its incorporation
98 into viral DNA. The lack of a 3'-OH group in the incorporated nucleotide analogue prevents the
99 formation of the 5' to 3' phosphodiester linkage essential for DNA chain elongation, and
100 therefore, the viral DNA growth is terminated. CBV-TP is a weak inhibitor of cellular DNA
101 polymerases α , β , and γ .

102 **Lamivudine:** Lamivudine is a synthetic nucleoside analogue. Intracellularly, lamivudine is
103 phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The
104 principal mode of action of 3TC-TP is inhibition of RT via DNA chain termination after
105 incorporation of the nucleotide analogue. 3TC-TP is a weak inhibitor of cellular DNA
106 polymerases α , β , and γ .

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

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113 Antiviral Activity:

114 **Abacavir:** The antiviral activity of abacavir against HIV-1 was evaluated against a T-cell
115 tropic laboratory strain HIV-1_{IIB} in lymphoblastic cell lines, a monocyte/macrophage tropic
116 laboratory strain HIV-1_{BaL} in primary monocytes/macrophages, and clinical isolates in peripheral
117 blood mononuclear cells. The concentration of drug necessary to effect viral replication by
118 50 percent (EC₅₀) ranged from 3.7 to 5.8 μ M (1 μ M = 0.28 mcg/mL) and 0.07 to 1.0 μ M against
119 HIV-1_{IIB} and HIV-1_{BaL}, respectively, and was $0.26 \pm 0.18 \mu$ M against 8 clinical isolates. The

120 EC₅₀ values of abacavir against different HIV-1 clades (A-G) ranged from 0.0015 to 1.05 μM,
121 and against HIV-2 isolates, from 0.024 to 0.49 μM. Abacavir had synergistic activity in cell
122 culture in combination with the nucleoside reverse transcriptase inhibitor (NRTI) zidovudine, the
123 non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, and the protease inhibitor
124 (PI) amprenavir; and additive activity in combination with the NRTIs didanosine, emtricitabine,
125 lamivudine, stavudine, tenofovir, and zalcitabine. Ribavirin (50 μM) had no effect on the anti-
126 HIV-1 activity of abacavir in cell culture.

127 **Lamivudine:** The antiviral activity of lamivudine against HIV-1 was assessed in a number of
128 cell lines (including monocytes and fresh human peripheral blood lymphocytes) using standard
129 susceptibility assays. EC₅₀ values were in the range of 0.003 to 15 μM (1 μM = 0.23 mcg/mL).
130 HIV-1 from therapy-naive subjects with no amino acid substitutions associated with resistance
131 gave median EC₅₀ values of 0.429 μM (range: 0.200 to 2.007 μM) from Virco (n = 92 baseline
132 samples from COLA40263) and 2.35 μM (1.37 to 3.68 μM) from Monogram Biosciences
133 (n = 135 baseline samples from ESS30009). The EC₅₀ values of lamivudine against different
134 HIV-1 clades (A-G) ranged from 0.001 to 0.120 μM, and against HIV-2 isolates from 0.003 to
135 0.120 μM in peripheral blood mononuclear cells. Ribavirin (50 μM) decreased the anti-HIV-1
136 activity of lamivudine by 3.5 fold in MT-4 cells.

137 **Zidovudine:** The antiviral activity of zidovudine against HIV-1 was assessed in a number of
138 cell lines (including monocytes and fresh human peripheral blood lymphocytes). The EC₅₀ and
139 EC₉₀ values for zidovudine were 0.01 to 0.49 μM (1 μM = 0.27 mcg/mL) and 0.1 to 9 μM,
140 respectively. HIV-1 from therapy-naive subjects with no amino acid substitutions associated with
141 resistance gave median EC₅₀ values of 0.011 μM (range: 0.005 to 0.110 μM) from Virco (n = 92
142 baseline samples from COLA40263) and 0.0017 μM (0.006 to 0.0340 μM) from Monogram
143 Biosciences (n = 135 baseline samples from ESS30009). The EC₅₀ values of zidovudine against
144 different HIV-1 clades (A-G) ranged from 0.00018 to 0.02 μM, and against HIV-2 isolates from
145 0.00049 to 0.004 μM. In cell culture drug combination studies, zidovudine demonstrates
146 synergistic activity with the NRTIs abacavir, didanosine, lamivudine, and zalcitabine; the
147 NNRTIs delavirdine and nevirapine; and the PIs indinavir, nelfinavir, ritonavir, and saquinavir;
148 and additive activity with interferon alfa. Ribavirin has been found to inhibit the phosphorylation
149 of zidovudine in cell culture.

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151 **Resistance:**

152 HIV-1 isolates with reduced sensitivity to abacavir, lamivudine, or zidovudine have been
153 selected in cell culture and were also obtained from patients treated with abacavir, lamivudine,
154 and zidovudine, or the combination of lamivudine and zidovudine.

155 **Abacavir:** Genotypic analysis of isolates selected in cell culture and recovered from
156 abacavir-treated patients demonstrated that amino acid substitutions K65R, L74V, Y115F, and
157 M184V/I in HIV-1 RT contributed to abacavir resistance. In a study of subjects receiving
158 abacavir once or twice daily in combination with lamivudine and efavirenz once daily, 39%
159 (7/18) of the isolates from patients who experienced virologic failure in the abacavir once-daily

160 arm had a >2.5-fold decrease in abacavir susceptibility with a median-fold decrease of 1.3 (range
161 0.5 to 11) compared with 29% (5/17) of the failure isolates in the twice-daily arm with a
162 median-fold decrease of 0.92 (range 0.7 to 13).

163 **Lamivudine:** Genotypic analysis of isolates selected in cell culture and recovered from
164 lamivudine-treated patients showed that the resistance was due to a specific amino acid
165 substitution in the HIV-1 RT at codon 184 changing the methionine to either isoleucine or valine
166 (M184V/I).

167 **Zidovudine:** Genotypic analyses of the isolates selected in cell culture and recovered from
168 zidovudine-treated patients showed mutations in the HIV-1 RT gene resulting in 6 amino acid
169 substitutions (M41L, D67N, K70R, L210W, T215Y or F, and K219Q) that confer zidovudine
170 resistance. In general, higher levels of resistance were associated with greater number of
171 mutations. In some patients harboring zidovudine-resistant virus at baseline, phenotypic
172 sensitivity to zidovudine was restored by 12 weeks of treatment with lamivudine and zidovudine.
173 Combination therapy with lamivudine plus zidovudine delayed the emergence of substitutions
174 conferring resistance to zidovudine.

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176 **Cross-Resistance:**

177 Cross-resistance has been observed among NRTIs.

178 **Abacavir:** Isolates containing abacavir resistance-associated amino acid substitutions,
179 namely, K65R, L74V, Y115F, and M184V, exhibited cross-resistance to didanosine,
180 emtricitabine, lamivudine, tenofovir, and zalcitabine in cell culture and in patients. The K65R
181 substitution can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, stavudine,
182 tenofovir, and zalcitabine; the L74V substitution can confer resistance to abacavir, didanosine,
183 and zalcitabine; and the M184V substitution can confer resistance to abacavir, didanosine,
184 emtricitabine, lamivudine, and zalcitabine. An increasing number of thymidine analogue
185 mutations (TAMs: M41L, D67N, K70R, L210W, T215Y/F, K219E/R/H/Q/N) is associated with
186 a progressive reduction in abacavir susceptibility.

187 **Lamivudine:** Cross-resistance to abacavir, didanosine, tenofovir, and zalcitabine has been
188 observed in some patients harboring lamivudine-resistant HIV-1 isolates. In some patients
189 treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple drugs,
190 including lamivudine, have emerged (see under Zidovudine below). Cross-resistance between
191 lamivudine and zidovudine has not been reported.

192 **Zidovudine:** In a study of 167 HIV-infected patients, isolates (n = 2) with multi-drug
193 resistance to didanosine, lamivudine, stavudine, zalcitabine, and zidovudine were recovered from
194 patients treated for ≥1 year with zidovudine plus didanosine or zidovudine plus zalcitabine. The
195 pattern of resistance-associated amino acid substitutions with such combination therapies was
196 different (A62V, V75I, F77L, F116Y, Q151M) from the pattern with zidovudine monotherapy,
197 with the Q151M substitution being most commonly associated with multi-drug resistance. The
198 substitution at codon 151 in combination with substitutions at 62, 75, 77, and 116 results in a
199 virus with reduced susceptibility to didanosine, lamivudine, stavudine, zalcitabine, and

200 zidovudine. TAMs are selected by zidovudine and confer cross-resistance to abacavir,
201 didanosine, stavudine, tenofovir, and zalcitabine.

202 **CLINICAL PHARMACOLOGY**

203 **Pharmacokinetics in Adults:**

204 **TRIZIVIR:** In a single-dose, 3-way crossover bioavailability study of 1 TRIZIVIR Tablet
205 versus 1 ZIAGEN Tablet (300 mg), 1 EPIVIR Tablet (150 mg), plus 1 RETROVIR Tablet
206 (300 mg) administered simultaneously in healthy subjects (n = 24), there was no difference in the
207 extent of absorption, as measured by the area under the plasma concentration-time curve (AUC)
208 and maximal peak concentration (C_{max}), of all 3 components. One TRIZIVIR Tablet was
209 bioequivalent to 1 ZIAGEN Tablet (300 mg), 1 EPIVIR Tablet (150 mg), plus 1 RETROVIR
210 Tablet (300 mg) following single-dose administration to fasting healthy subjects (n = 24).

211 **Abacavir:** Following oral administration, abacavir is rapidly absorbed and extensively
212 distributed. Binding of abacavir to human plasma proteins is approximately 50%. Binding of
213 abacavir to plasma proteins was independent of concentration. Total blood and plasma
214 drug-related radioactivity concentrations are identical, demonstrating that abacavir readily
215 distributes into erythrocytes. The primary routes of elimination of abacavir are metabolism by
216 alcohol dehydrogenase to form the 5'-carboxylic acid and glucuronyl transferase to form the
217 5'-glucuronide.

218 **Lamivudine:** Following oral administration, lamivudine is rapidly absorbed and extensively
219 distributed. Binding to plasma protein is low. Approximately 70% of an intravenous dose of
220 lamivudine is recovered as unchanged drug in the urine. Metabolism of lamivudine is a minor
221 route of elimination. In humans, the only known metabolite is the trans-sulfoxide metabolite
222 (approximately 5% of an oral dose after 12 hours).

223 **Zidovudine:** Following oral administration, zidovudine is rapidly absorbed and extensively
224 distributed. Binding to plasma protein is low. Zidovudine is eliminated primarily by hepatic
225 metabolism. The major metabolite of zidovudine is 3'-azido-3'-deoxy-5'-O- β -D-
226 glucopyranuronosylthymidine (GZDV). GZDV area under the curve (AUC) is about 3-fold
227 greater than the zidovudine AUC. Urinary recovery of zidovudine and GZDV accounts for 14%
228 and 74% of the dose following oral administration, respectively. A second metabolite, 3'-amino-
229 3'-deoxythymidine (AMT), has been identified in plasma. The AMT AUC was one fifth of the
230 zidovudine AUC.

231 In humans, abacavir, lamivudine, and zidovudine are not significantly metabolized by
232 cytochrome P450 enzymes.

233 The pharmacokinetic properties of abacavir, lamivudine, and zidovudine in fasting patients
234 are summarized in Table 1.

235

236 **Table 1. Pharmacokinetic Parameters* for Abacavir, Lamivudine, and Zidovudine in**
 237 **Adults**

Parameter	Abacavir		Lamivudine		Zidovudine	
Oral bioavailability (%)	86 ± 25	n = 6	86 ± 16	n = 12	64 ± 10	n = 5
Apparent volume of distribution (L/kg)	0.86 ± 0.15	n = 6	1.3 ± 0.4	n = 20	1.6 ± 0.6	n = 8
Systemic clearance (L/hr/kg)	0.80 ± 0.24	n = 6	0.33 ± 0.06	n = 20	1.6 ± 0.6	n = 6
Renal clearance (L/hr/kg)	.007 ± .008	n = 6	0.22 ± 0.06	n = 20	0.34 ± 0.05	n = 9
Elimination half-life (hr) [†]	1.45 ± 0.32	n = 20	5 to 7		0.5 to 3	

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

239 [†]Approximate range.

240

241 **Effect of Food on Absorption of TRIZIVIR:**

242 TRIZIVIR may be administered with or without food. Administration with food in a
 243 single-dose bioavailability study resulted in lower C_{max}, similar to results observed previously for
 244 the reference formulations. The average [90% CI] decrease in abacavir, lamivudine, and
 245 zidovudine C_{max} was 32% [24% to 38%], 18% [10% to 25%], and 28% [13% to 40%],
 246 respectively, when administered with a high-fat meal, compared with administration under fasted
 247 conditions. Administration of TRIZIVIR with food did not alter the extent of abacavir,
 248 lamivudine, and zidovudine absorption (AUC), as compared with administration under fasted
 249 conditions (n = 24).

250

251 **Special Populations:**

252 ***Impaired Renal Function:***

253 **TRIZIVIR:** Because lamivudine and zidovudine require dose adjustment in the presence of
 254 renal insufficiency, TRIZIVIR is not recommended for use in patients with creatinine clearance
 255 <50 mL/min (see PRECAUTIONS).

256 ***Impaired Hepatic Function:***

257 **TRIZIVIR:** A reduction in the daily dose of zidovudine may be necessary in patients with
 258 mild to moderate impaired hepatic function or liver cirrhosis. Abacavir is contraindicated in
 259 patients with moderate to severe hepatic impairment and dose reduction is required in patients
 260 with mild hepatic impairment. Because TRIZIVIR is a fixed-dose combination that cannot be
 261 adjusted for this patient population, TRIZIVIR is contraindicated for patients with impaired
 262 hepatic function.

263 **Pregnancy:** See PRECAUTIONS: Pregnancy.

264 **Abacavir and Lamivudine:** No data are available on the pharmacokinetics of abacavir
 265 or lamivudine during pregnancy.

266 **Zidovudine:** Zidovudine pharmacokinetics have been studied in a Phase 1 study of
 267 8 women during the last trimester of pregnancy. As pregnancy progressed, there was no evidence
 268 of drug accumulation. The pharmacokinetics of zidovudine were similar to that of nonpregnant

269 adults. Consistent with passive transmission of the drug across the placenta, zidovudine
270 concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at
271 delivery. Although data are limited, methadone maintenance therapy in 5 pregnant women did
272 not appear to alter zidovudine pharmacokinetics. In a nonpregnant adult population, a potential
273 for interaction has been identified (see CLINICAL PHARMACOLOGY: Drug Interactions).

274 **Nursing Mothers:** See PRECAUTIONS: Nursing Mothers.

275 **Abacavir:** No data are available on the pharmacokinetics of abacavir in nursing mothers.

276 **Lamivudine:** Samples of breast milk obtained from 20 mothers receiving lamivudine
277 monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice daily and
278 300 mg zidovudine twice daily) had measurable concentrations of lamivudine.

279 **Zidovudine:** After administration of a single dose of 200 mg zidovudine to
280 13 HIV-infected women, the mean concentration of zidovudine was similar in human milk and
281 serum.

282 **Pediatric Patients:**

283 **TRIZIVIR:** TRIZIVIR is not intended for use in pediatric patients. TRIZIVIR should not be
284 administered to adolescents who weigh less than 40 kg because it is a fixed-dose tablet that
285 cannot be dose adjusted for this patient population (see PRECAUTIONS: Pediatric Use).

286 **Geriatric Patients:** The pharmacokinetics of abacavir, lamivudine, and zidovudine have not
287 been studied in patients over 65 years of age.

288 **Gender:**

289 **Abacavir:** A population pharmacokinetic analysis in HIV-1-infected male (n = 304) and
290 female (n = 67) patients showed no gender differences in abacavir AUC normalized for lean
291 body weight.

292 **Lamivudine and Zidovudine:** A pharmacokinetic study in healthy male (n = 12) and
293 female (n = 12) subjects showed no gender differences in zidovudine exposure (AUC_∞) or
294 lamivudine (AUC_∞) normalized for body weight.

295 **Race:**

296 **Abacavir:** There are no significant differences between blacks and Caucasians in abacavir
297 pharmacokinetics.

298 **Lamivudine:** There are no significant racial differences in lamivudine pharmacokinetics.

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

301

302 **Drug Interactions:** See PRECAUTIONS: Drug Interactions. The drug interactions described
303 are based on studies conducted with the individual nucleoside analogues. In humans, abacavir,
304 lamivudine, and zidovudine are not significantly metabolized by cytochrome P450 enzymes;
305 therefore, it is unlikely that clinically significant drug interactions will occur with drugs
306 metabolized through these pathways.

307 **Abacavir:** Due to the common metabolic pathways of abacavir and zidovudine via
308 glucuronyl transferase, 15 HIV-1-infected patients were enrolled in a crossover study evaluating

309 single doses of abacavir (600 mg), lamivudine (150 mg), and zidovudine (300 mg) alone or in
310 combination. Analysis showed no clinically relevant changes in the pharmacokinetics of abacavir
311 with the addition of lamivudine or zidovudine or the combination of lamivudine and zidovudine.
312 Lamivudine exposure (AUC decreased 15%) and zidovudine exposure (AUC increased 10%) did
313 not show clinically relevant changes with concurrent abacavir.

314 In a study of 11 HIV-1-infected patients receiving methadone-maintenance therapy (40 mg
315 and 90 mg daily), with 600 mg of ZIAGEN twice daily (twice the currently recommended dose),
316 oral methadone clearance increased 22% (90% CI: 6% to 42%). This alteration will not result in
317 a methadone dose modification in the majority of patients; however, an increased methadone
318 dose may be required in a small number of patients.

319 **Lamivudine and Zidovudine:** No clinically significant alterations in lamivudine or
320 zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-1-infected adult patients
321 given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine
322 (300 mg q 12 hr).

323

324 **Table 2. Effect of Coadministered Drugs on Abacavir, Lamivudine, and Zidovudine AUC***
Note: ROUTINE DOSE MODIFICATION OF ABACAVIR, LAMIVUDINE, AND ZIDOVUDINE IS NOT WARRANTED WITH COADMINISTRATION OF THE FOLLOWING 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	↑10%	95% CI: 1% to 20%	↔
Trimethoprim 160 mg/ Sulfamethoxazole 800 mg daily x 5 days	single 300 mg	14	↑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	↑31%	Range 23% to 78% [†]	↔
Fluconazole 400 mg daily	200 mg q 8 hr	12	↑74%	95% CI: 54% to 98%	Not Reported
Methadone 30 to 90 mg daily	200 mg q 4 hr	9	↑43%	Range 16% to 64% [†]	↔
Nelfinavir 750 mg q 8 hr x 7 to 10 days	single 200 mg	11	↓35%	Range 28% to 41%	↔
Probenecid 500 mg q 6 hr x 2 days	2 mg/kg q 8 hr x 3 days	3	↑ 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	↓ 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	↑80%	Range 64% to 130% [†]	Not Assessed
Drugs That May Alter Abacavir Blood Concentrations					

Coadministered Drug and Dose	Abacavir Dose	n	Abacavir Concentrations		Concentration of Coadministered Drug
			AUC	Variability	
Ethanol 0.7 g/kg	single 600 mg	24	↑41%	90% CI: 35% to 48%	↔

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

327 *See PRECAUTIONS: Drug Interactions for additional information on drug interactions.

328 †Estimated range of percent difference.

329

330 **Ribavirin:** In vitro data indicate ribavirin reduces phosphorylation of lamivudine, stavudine,
331 and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular
332 triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of
333 HIV-1/HCV virologic suppression) interaction was observed when ribavirin and lamivudine
334 (n = 18), stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug
335 regimen to HIV-1/HCV co-infected patients (see WARNINGS).

336 INDICATIONS AND USAGE

337 **TRIZIVIR is indicated in combination with other antiretrovirals or alone for the**
338 **treatment of HIV-1 infection.**

339 **Additional important information on the use of TRIZIVIR for treatment of HIV-1**
340 **infection:**

- 341 • TRIZIVIR is one of multiple products containing abacavir. Before starting TRIZIVIR,
342 review medical history for prior exposure to any abacavir-containing product in order to
343 avoid reintroduction in a patient with a history of hypersensitivity to abacavir.
- 344 • Limited data exist on the use of TRIZIVIR alone in patients with higher baseline viral load
345 levels (>100,000 copies/mL, see Description of Clinical Studies).

346

347 Description of Clinical Studies:

348 **TRIZIVIR:** The following study was conducted with the individual components of TRIZIVIR
349 (see CLINICAL PHARMACOLOGY for information about bioequivalence of TRIZIVIR).

350 **CNA3005** was a multicenter, double-blind, controlled study in which 562 HIV-1-infected,
351 therapy-naive adults were randomized to receive either ZIAGEN (300 mg twice daily) plus
352 COMBIVIR® (lamivudine 150 mg/zidovudine 300 mg twice daily), or indinavir (800 mg 3 times
353 a day) plus COMBIVIR twice daily. The study was stratified at randomization by pre-entry
354 plasma HIV-1 RNA 10,000 to 100,000 copies/mL and plasma HIV-1 RNA >100,000 copies/mL.
355 Study participants were male (87%), Caucasian (73%), black (15%), and Hispanic (9%). At
356 baseline the median age was 36 years, the median pretreatment CD4+ cell count was
357 360 cells/mm³, and median plasma HIV-1 RNA was 4.8 log₁₀ copies/mL. Proportions of patients

358 with plasma HIV-1 RNA <400 copies/mL (using Roche AMPLICOR HIV-1 MONITOR® Test)
 359 through 48 weeks of treatment are summarized in Table 3.

360

361 **Table 3. Outcomes of Randomized Treatment Through Week 48 (CNA3005)**

Outcome	ZIAGEN plus Lamivudine/Zidovudine (n = 262)	Indinavir plus Lamivudine/Zidovudine (n = 265)
Responder*	49%	50%
Virologic failure†	31%	28%
Discontinued due to adverse reactions	10%	12%
Discontinued due to other reasons‡	11%	10%

362 * Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL.

363 † Includes viral rebound and failure to achieve confirmed <400 copies/mL by Week 48.

364 ‡ Includes consent withdrawn, lost to follow-up, protocol violations, those with missing data,
 365 clinical progression, and other.

366

367 Treatment response by plasma HIV-1 RNA strata is shown in Table 4.

368

369 **Table 4. Proportions of Responders Through Week 48 By Screening Plasma HIV-1 RNA**
 370 **Levels (CNA3005)**

Screening HIV-1 RNA (copies/mL)	ZIAGEN plus Lamivudine/Zidovudine (n = 262)		Indinavir plus Lamivudine/Zidovudine (n = 265)	
	<400 copies/mL	n	<400 copies/mL	n
≥10,000 - ≤100,000	50%	166	48%	165
>100,000	48%	96	52%	100

371

372 In subjects with baseline viral load >100,000 copies/mL, percentages of patients with HIV-1
 373 RNA levels <50 copies/mL were 31% in the group receiving abacavir vs. 45% in the group
 374 receiving indinavir.

375 Through Week 48, an overall mean increase in CD4+ cell count of about 150 cells/mm³ was
 376 observed in both treatment arms. Through Week 48, 9 subjects (3.4%) in the group receiving
 377 abacavir sulfate (6 CDC classification C events and 3 deaths) and 3 subjects (1.5%) in the group
 378 receiving indinavir (2 CDC classification C events and 1 death) experienced clinical disease
 379 progression.

380 **CONTRAINDICATIONS**

381 **TRIZIVIR Tablets are contraindicated in patients with previously demonstrated**
 382 **hypersensitivity to abacavir or to any other component of the product (see WARNINGS).**

383 **NEVER restart TRIZIVIR or any other abacavir-containing product following a**
384 **hypersensitivity reaction to abacavir, regardless of HLA-B*5701 status (see WARNINGS,**
385 **PRECAUTIONS, and ADVERSE REACTIONS).**

386 TRIZIVIR Tablets are contraindicated in patients with hepatic impairment (see CLINICAL
387 PHARMACOLOGY).

388 **WARNINGS**

389 **Hypersensitivity Reaction: Serious and sometimes fatal hypersensitivity reactions have**
390 **been associated with TRIZIVIR and other abacavir-containing products. Patients who**
391 **carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to**
392 **abacavir. Prior to initiating therapy with abacavir, screening for the HLA-B*5701 allele is**
393 **recommended; this approach has been found to decrease the risk of a hypersensitivity**
394 **reaction. Screening is also recommended prior to reinitiation of abacavir in patients of**
395 **unknown HLA-B*5701 status who have previously tolerated abacavir. For**
396 **HLA-B*5701-positive patients, treatment with an abacavir-containing regimen is not**
397 **recommended and should be considered only with close medical supervision and under**
398 **exceptional circumstances when the potential benefit outweighs the risk.**

399 **HLA-B*5701-negative patients may develop a hypersensitivity reaction to abacavir;**
400 **however, this occurs significantly less frequently than in HLA-B*5701-positive patients.**
401 **Regardless of HLA-B*5701 status, permanently discontinue TRIZIVIR if hypersensitivity**
402 **cannot be ruled out, even when other diagnoses are possible.**

403 **Important information on signs and symptoms of hypersensitivity, as well as clinical**
404 **management, is presented below.**

405 ***Signs and Symptoms of Hypersensitivity:*** Hypersensitivity to abacavir is a multi-organ
406 clinical syndrome usually characterized by a sign or symptom in 2 or more of the following
407 groups.

408 **Group 1: Fever**

409 **Group 2: Rash**

410 **Group 3: Gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain)**

411 **Group 4: Constitutional (including generalized malaise, fatigue, or achiness)**

412 **Group 5: Respiratory (including dyspnea, cough, or pharyngitis)**

413

414 Hypersensitivity to abacavir following the presentation of a single sign or symptom has been
415 reported infrequently.

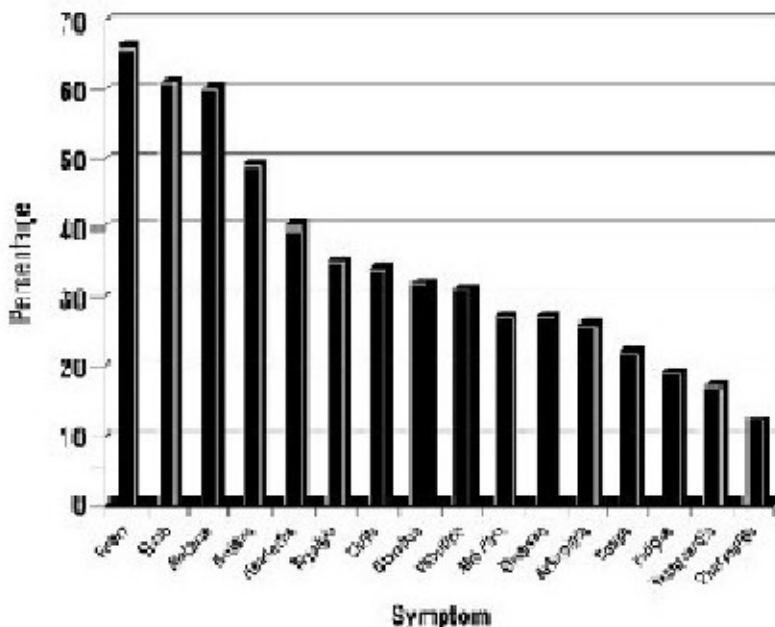
416 Hypersensitivity to abacavir was reported in approximately 8% of 2,670 patients (n = 206) in
417 9 clinical trials (range: 2% to 9%) with enrollment from November 1999 to February 2002. Data
418 on time to onset and symptoms of suspected hypersensitivity were collected on a detailed data
419 collection module. The frequencies of symptoms are shown in Figure 1. Symptoms usually
420 appeared within the first 6 weeks of treatment with abacavir, although the reaction may occur at

421 any time during therapy. Median time to onset was 9 days; 89% appeared within the first
422 6 weeks; 95% of patients reported symptoms from 2 or more of the 5 groups listed above.

423 A recent study with ZIAGEN used double-blind ascertainment of suspected hypersensitivity
424 reactions. During the blinded portion of the study, suspected hypersensitivity to abacavir was
425 reported by investigators in 9% of 324 patients in the abacavir group and 3% of 325 patients in
426 the zidovudine group.

427

428 **Figure 1. Hypersensitivity-Related Symptoms Reported with**
429 **≥10% Frequency in Clinical Trials (n = 206 Patients)**



430

431

432 Other less common signs and symptoms of hypersensitivity include lethargy, myolysis,
433 edema, abnormal chest x-ray findings (predominantly infiltrates, which can be localized), and
434 paresthesia. Anaphylaxis, liver failure, renal failure, hypotension, adult respiratory distress
435 syndrome, respiratory failure, and death have occurred in association with hypersensitivity
436 reactions.

437 Physical findings associated with hypersensitivity to abacavir in some patients include
438 lymphadenopathy, mucous membrane lesions (conjunctivitis and mouth ulcerations), and rash.
439 The rash usually appears maculopapular or urticarial, but may be variable in appearance. There
440 have been reports of erythema multiforme. Hypersensitivity reactions have occurred without
441 rash.

442 Laboratory abnormalities associated with hypersensitivity to abacavir in some patients include
443 elevated liver function tests, elevated creatine phosphokinase, elevated creatinine, and
444 lymphopenia.

445 ***Clinical Management of Hypersensitivity: Discontinue TRIZIVIR as soon as a***
446 **hypersensitivity reaction is suspected. To minimize the risk of a life-threatening**

447 hypersensitivity reaction, permanently discontinue TRIZIVIR if hypersensitivity cannot be
448 ruled out, even when other diagnoses are possible (e.g., acute onset respiratory diseases
449 such as pneumonia, bronchitis, pharyngitis, or influenza; gastroenteritis; or reactions to
450 other medications).

451 **Following a hypersensitivity reaction to abacavir, NEVER restart TRIZIVIR or any**
452 **other abacavir-containing product because more severe symptoms can occur within hours**
453 **and may include life-threatening hypotension and death.**

454 When therapy with TRIZIVIR has been discontinued for reasons other than symptoms of a
455 hypersensitivity reaction, and if reinitiation of abacavir is under consideration, carefully evaluate
456 the reason for discontinuation to ensure that the patient did not have symptoms of a
457 hypersensitivity reaction. If the patient is of unknown HLA-B*5701 status, screening for the
458 allele is recommended prior to reinitiation of TRIZIVIR.

459 If hypersensitivity cannot be ruled out, DO NOT reintroduce TRIZIVIR or any other
460 abacavir-containing product. Even in the absence of the HLA-B*5701 allele, it is important to
461 permanently discontinue abacavir and not rechallenge with abacavir if a hypersensitivity reaction
462 cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction.

463 If symptoms consistent with hypersensitivity are not identified, reintroduction can be
464 undertaken with continued monitoring for symptoms of a hypersensitivity reaction. Make
465 patients aware that a hypersensitivity reaction can occur with reintroduction of abacavir and that
466 abacavir reintroduction needs to be undertaken only if medical care can be readily accessed by
467 the patient or others.

468 **Risk Factor: HLA-B*5701 Allele:** Studies have shown that carriage of the HLA-B*5701
469 allele is associated with a significantly increased risk of a hypersensitivity reaction to abacavir.

470 CNA106030 (PREDICT-1), a randomized, double-blind study, evaluated the clinical utility of
471 prospective HLA-B*5701 screening on the incidence of abacavir hypersensitivity reaction in
472 abacavir-naive HIV-1-infected adults (n = 1,650). In this study, use of pre-therapy screening for
473 the HLA-B*5701 allele and exclusion of subjects with this allele reduced the incidence of
474 clinically suspected abacavir hypersensitivity reactions from 7.8% (66/847) to 3.4% (27/803).
475 Based on this study, it is estimated that 61% of patients with the HLA-B*5701 allele will
476 develop a clinically suspected hypersensitivity reaction during the course of abacavir treatment
477 compared with 4% of patients who do not have the HLA-B*5701 allele.

478 Screening for carriage of the HLA-B*5701 allele is recommended prior to initiating treatment
479 with abacavir. Screening is also recommended prior to reinitiation of abacavir in patients of
480 unknown HLA-B*5701 status who have previously tolerated abacavir. For
481 HLA-B*5701-positive patients, initiating or reinitiating treatment with an abacavir-containing
482 regimen is not recommended and should be considered only with close medical supervision and
483 under exceptional circumstances where potential benefit outweighs the risk.

484 Skin patch testing is used as a research tool and should not be used to aid in the clinical
485 diagnosis of abacavir hypersensitivity.

486 In any patient treated with abacavir, the clinical diagnosis of hypersensitivity reaction must
487 remain the basis of clinical decision-making. Even in the absence of the HLA-B*5701 allele, it is
488 important to permanently discontinue abacavir and not rechallenge with abacavir if a
489 hypersensitivity reaction cannot be ruled out on clinical grounds, due to the potential for a severe
490 or even fatal reaction.

491 **Abacavir Hypersensitivity Reaction Registry:** An Abacavir Hypersensitivity Registry
492 has been established to facilitate reporting of hypersensitivity reactions and collection of
493 information on each case. Physicians should register patients by calling 1-800-270-0425.
494

495 **Lactic Acidosis/Severe Hepatomegaly With Steatosis:** Lactic acidosis and severe
496 hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside
497 analogues alone or in combination, including abacavir, lamivudine, zidovudine, and other
498 antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside
499 exposure may be risk factors. Particular caution should be exercised when administering
500 TRIZIVIR to any patient with known risk factors for liver disease; however, cases have also
501 been reported in patients with no known risk factors. Treatment with TRIZIVIR should be
502 suspended in any patient who develops clinical or laboratory findings suggestive of lactic
503 acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in
504 the absence of marked transaminase elevations).
505

506 **Bone Marrow Suppression:** Since TRIZIVIR contains zidovudine, TRIZIVIR should be
507 used with caution in patients who have bone marrow compromise evidenced by granulocyte
508 count $<1,000$ cells/mm³ or hemoglobin <9.5 g/dL. Frequent blood counts are strongly
509 recommended in patients with advanced HIV-1 disease who are treated with TRIZIVIR. For
510 HIV-1-infected individuals and patients with asymptomatic or early HIV-1 disease, periodic
511 blood counts are recommended.
512

513 **Myopathy:** Myopathy and myositis, with pathological changes similar to that produced by
514 HIV-1 disease, have been associated with prolonged use of zidovudine, and therefore may occur
515 with therapy with TRIZIVIR.
516

517 **Posttreatment Exacerbations of Hepatitis:** In clinical trials in non-HIV-1-infected
518 patients treated with lamivudine for chronic HBV, clinical and laboratory evidence of
519 exacerbations of hepatitis have occurred after discontinuation of lamivudine. These
520 exacerbations have been detected primarily by serum ALT elevations in addition to
521 re-emergence of HBV DNA. Although most events appear to have been self-limited, fatalities
522 have been reported in some cases. Similar events have been reported from post-marketing
523 experience after changes from lamivudine-containing HIV-1 treatment regimens to
524 non-lamivudine-containing regimens in patients infected with both HIV-1 and HBV. The causal
525 relationship to discontinuation of lamivudine treatment is unknown. Patients should be closely

526 monitored with both clinical and laboratory follow-up for at least several months after stopping
527 treatment. There is insufficient evidence to determine whether re-initiation of lamivudine alters
528 the course of posttreatment exacerbations of hepatitis.

529
530 **Use With Interferon- and Ribavirin-Based Regimens:** In vitro studies have shown
531 ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine
532 and zidovudine, components of TRIZIVIR. Although no evidence of a pharmacokinetic or
533 pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when
534 ribavirin was coadministered with lamivudine or zidovudine in HIV-1/HCV co-infected patients
535 (see CLINICAL PHARMACOLOGY: Drug Interactions), **hepatic decompensation (some**
536 **fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral**
537 **therapy for HIV-1 and interferon alfa with or without ribavirin.** Patients receiving interferon
538 alfa with or without ribavirin and TRIZIVIR should be closely monitored for
539 treatment-associated toxicities, especially hepatic decompensation, neutropenia, and anemia.
540 Discontinuation of TRIZIVIR should be considered as medically appropriate. Dose reduction or
541 discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening
542 clinical toxicities are observed, including hepatic decompensation (e.g., Childs Pugh >6) (see the
543 complete prescribing information for interferon and ribavirin).

544
545 **Other:** TRIZIVIR contains fixed doses of 3 nucleoside analogues: abacavir, lamivudine, and
546 zidovudine and should not be administered concomitantly with abacavir, lamivudine,
547 emtricitabine, or zidovudine. TRIZIVIR should also not be administered concomitantly with the
548 fixed-dose combination drugs: lamivudine/zidovudine (COMBIVIR), abacavir and lamivudine
549 (EPZICOM[®]), or emtricitabine and tenofovir (TRUVADA[®]).

550 Because TRIZIVIR is a fixed-dose tablet, it should not be prescribed for adolescents who
551 weigh less than 40 kg or other patients requiring dosage adjustment.

552 The complete prescribing information for all agents being considered for use with TRIZIVIR
553 should be consulted before combination therapy with TRIZIVIR is initiated.

554 **PRECAUTIONS**

555 **Therapy-Experienced Patients:**

556 **Abacavir:** In clinical trials, patients with prolonged prior NRTI exposure or who had HIV-1
557 isolates that contained multiple mutations conferring resistance to NRTIs had limited response to
558 abacavir. The potential for cross-resistance between abacavir and other NRTIs should be
559 considered when choosing new therapeutic regimens in therapy-experienced patients (see
560 MICROBIOLOGY: Cross-Resistance).

561

562 **Patients With HIV-1 and Hepatitis B Virus Co-infection:**

563 **Lamivudine:** Safety and efficacy of lamivudine have not been established for treatment of
564 chronic hepatitis B in patients dually infected with HIV-1 and HBV. In non-HIV-1-infected

565 patients treated with lamivudine for chronic hepatitis B, emergence of lamivudine-resistant HBV
566 has been detected and has been associated with diminished treatment response (see EPIVIR-
567 HBV[®] package insert for additional information). Emergence of hepatitis B virus variants
568 associated with resistance to lamivudine has also been reported in HIV-1-infected patients who
569 have received lamivudine-containing antiretroviral regimens in the presence of concurrent
570 infection with hepatitis B virus.

571

572 **Patients With Impaired Renal Function:**

573 **TRIZIVIR:** Since TRIZIVIR is a fixed-dose tablet and the dosage of the individual
574 components cannot be altered, patients with creatinine clearance <50 mL/min should not receive
575 TRIZIVIR.

576

577 **Patients With Impaired Hepatic Function:**

578 **TRIZIVIR:** TRIZIVIR is contraindicated in patients with hepatic impairment since it is a
579 fixed-dose tablet and the dosage of the individual components cannot be altered.

580

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

587

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

593

594 **Myocardial Infarction:** In a published prospective, observational, epidemiological study
595 designed to investigate the rate of myocardial infarction in patients on combination antiretroviral
596 therapy, the use of abacavir within the previous 6 months was correlated with an increased risk
597 of myocardial infarction (MI).¹ In a sponsor-conducted pooled analysis of clinical trials, no
598 excess risk of MI was observed in abacavir-treated subjects as compared with control subjects. In
599 totality, the available data from the observational cohort and from clinical trials are inconclusive.

600 As a precaution, the underlying risk of coronary heart disease should be considered when
601 prescribing antiretroviral therapies, including abacavir, and action taken to minimize all
602 modifiable risk factors (e.g., hypertension, hyperlipidemia, diabetes mellitus, and smoking).

603

604 **Information for Patients:**

- 605 **Abacavir: Hypersensitivity Reaction:** Inform patients:
- 606 • that a Medication Guide and Warning Card summarizing the symptoms of the abacavir
 - 607 hypersensitivity reaction and other product information will be dispensed by the
 - 608 pharmacist with each new prescription and refill of TRIZIVIR, and encourage the
 - 609 patient to read the Medication Guide and Warning Card every time to obtain any new
 - 610 information that may be present about TRIZIVIR. (The complete text of the
 - 611 Medication Guide is reprinted at the end of this document.)
 - 612 • to carry the Warning Card with them.
 - 613 • how to identify a hypersensitivity reaction (see WARNINGS and MEDICATION GUIDE).
 - 614 • that if they develop symptoms consistent with a hypersensitivity reaction they should call
 - 615 their doctor right away to determine if they should stop taking TRIZIVIR.
 - 616 • that a hypersensitivity reaction can worsen and lead to hospitalization or death if TRIZIVIR
 - 617 is not immediately discontinued.
 - 618 • to not restart TRIZIVIR or any other abacavir-containing product following a
 - 619 hypersensitivity reaction because more severe symptoms can occur within hours and
 - 620 may include life-threatening hypotension and death.
 - 621 • that a hypersensitivity reaction is usually reversible if it is detected promptly and TRIZIVIR
 - 622 is stopped right away.
 - 623 • that if they have interrupted TRIZIVIR for reasons other than symptoms of hypersensitivity
 - 624 (for example, those who have an interruption in drug supply), a serious or fatal
 - 625 hypersensitivity reaction may occur with reintroduction of abacavir.
 - 626 • to not restart TRIZIVIR or any other abacavir-containing product without medical
 - 627 consultation and that restarting abacavir needs to be undertaken only if medical care can be
 - 628 readily accessed by the patient or others.
 - 629 • TRIZIVIR should not be coadministered with COMBIVIR, EMTRIVA™, EPIVIR,
 - 630 EPIVIR-HBV, EPZICOM, RETROVIR, TRUVADA, or ZIAGEN.

631 **Lamivudine:** Patients co-infected with HIV-1 and HBV should be informed that

632 deterioration of liver disease has occurred in some cases when treatment with lamivudine was

633 discontinued. Patients should be advised to discuss any changes in regimen with their physician.

634 **Zidovudine:** Patients should be informed that the important toxicities associated with

635 zidovudine are neutropenia and/or anemia. They should be told of the extreme importance of

636 having their blood counts followed closely while on therapy, especially for patients with

637 advanced HIV-1 disease.

638 **TRIZIVIR:** Inform patients that some HIV-1 medicines, including TRIZIVIR can cause a rare,

639 but serious condition called lactic acidosis with liver enlargement (hepatomegaly).

640 TRIZIVIR is not a cure for HIV-1 infection and patients may continue to experience illnesses

641 associated with HIV-1 infection, including opportunistic infections. Patients should remain under

642 the care of a physician when using TRIZIVIR. Advise patients that the use of TRIZIVIR has not

643 been shown to reduce the risk of transmission of HIV-1 to others through sexual contact or blood

644 contamination.

645 Inform patients that redistribution or accumulation of body fat may occur in patients receiving
646 antiretroviral therapy and that the cause and long-term health effects of these conditions are not
647 known at this time.

648 TRIZIVIR Tablets are for oral ingestion only.

649 Patients should be advised of the importance of taking TRIZIVIR exactly as it is prescribed.

650

651 **Drug Interactions:**

652 **TRIZIVIR:** No clinically significant changes to pharmacokinetic parameters were observed
653 for abacavir, lamivudine, or zidovudine when administered together.

654 **Abacavir:** Abacavir has no effect on the pharmacokinetic properties of ethanol. Ethanol
655 decreases the elimination of abacavir causing an increase in overall exposure (see CLINICAL
656 PHARMACOLOGY: Drug Interactions).

657 The addition of methadone has no clinically significant effect on the pharmacokinetic
658 properties of abacavir. In a study of 11 HIV-1-infected patients receiving
659 methadone-maintenance therapy (40 mg and 90 mg daily), with 600 mg of ZIAGEN twice daily
660 (twice the currently recommended dose), oral methadone clearance increased 22% (90% CI: 6%
661 to 42%). This alteration will not result in a methadone dose modification in the majority of
662 patients; however, an increased methadone dose may be required in a small number of patients.

663 **Lamivudine:** Trimethoprim (TMP) 160 mg/sulfamethoxazole (SMX) 800 mg once daily has
664 been shown to increase lamivudine exposure (AUC). The effect of higher doses of TMP/SMX on
665 lamivudine pharmacokinetics has not been investigated (see CLINICAL PHARMACOLOGY).

666 Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another.
667 Therefore, use of TRIZIVIR in combination with zalcitabine is not recommended.

668 **Zidovudine:** Coadministration of ganciclovir, interferon-alfa, and other bone marrow
669 suppressive or cytotoxic agents may increase the hematologic toxicity of zidovudine.
670 Concomitant use of zidovudine with stavudine should be avoided since an antagonistic
671 relationship has been demonstrated in vitro. In addition, concomitant use of zidovudine with
672 doxorubicin or ribavirin should be avoided because an antagonistic relationship has also been
673 demonstrated in vitro.

674 See CLINICAL PHARMACOLOGY for additional drug interactions.

675

676 **Carcinogenesis, Mutagenesis, and Impairment of Fertility:**

677 **Carcinogenicity:**

678 **Abacavir:** Abacavir was administered orally at 3 dosage levels to separate groups of mice
679 and rats in 2-year carcinogenicity studies. Results showed an increase in the incidence of
680 malignant and non-malignant tumors. Malignant tumors occurred in the preputial gland of males
681 and the clitoral gland of females of both species, and in the liver of female rats. In addition,
682 non-malignant tumors also occurred in the liver and thyroid gland of female rats.

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

686 **Zidovudine:** Zidovudine was administered orally at 3 dosage levels to separate groups of
687 mice and rats (60 females and 60 males in each group). Initial single daily doses were 30, 60, and
688 120 mg/kg/day in mice and 80, 220, and 600 mg/kg/day in rats. The doses in mice were reduced
689 to 20, 30, and 40 mg/kg/day after day 90 because of treatment-related anemia, whereas in rats
690 only the high dose was reduced to 450 mg/kg per day on day 91 and then to 300 mg/kg/day on
691 day 279.

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

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

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

702 Two transplacental carcinogenicity studies were conducted in mice. One study administered
703 zidovudine at doses of 20 mg/kg/day or 40 mg/kg/day from gestation day 10 through parturition
704 and lactation with dosing continuing in offspring for 24 months postnatally. At these doses,
705 exposures were approximately 3 times the estimated human exposure at the recommended doses.
706 After 24 months at the 40-mg/kg/day dose, an increase in incidence of vaginal tumors was noted
707 with no increase in tumors in the liver or lung or any other organ in either gender. These findings
708 are consistent with results of the standard oral carcinogenicity study in mice, as described earlier.
709 A second study administered zidovudine at maximum tolerated doses of 12.5 mg/day or
710 25 mg/day (~1,000 mg/kg nonpregnant body weight or ~450 mg/kg of term body weight) to
711 pregnant mice from days 12 through 18 of gestation. There was an increase in the number of
712 tumors in the lung, liver, and female reproductive tracts in the offspring of mice receiving the
713 higher dose level of zidovudine.

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

716 **Mutagenicity:**

717 **Abacavir:** Abacavir induced chromosomal aberrations both in the presence and absence
718 of metabolic activation in an in vitro cytogenetic study in human lymphocytes. Abacavir was
719 mutagenic in the absence of metabolic activation, although it was not mutagenic in the presence
720 of metabolic activation in an L5178Y/TK^{+/-} mouse lymphoma assay. Abacavir was clastogenic
721 in males and not clastogenic in females in an in vivo mouse bone marrow micronucleus assay.

722 Abacavir was not mutagenic in bacterial mutagenicity assays in the presence and absence of
723 metabolic activation.

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

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

733 **Impairment of Fertility:**

734 **Abacavir:** Abacavir had no adverse effects on the mating performance or fertility of male
735 and female rats at a dose approximately 8 times the human exposure at the recommended dose
736 based on body surface area comparisons.

737 **Lamivudine:** In a study of reproductive performance, lamivudine, administered to male
738 and female rats at doses up to 130 times the usual adult dose based on body surface area
739 considerations, revealed no evidence of impaired fertility judged by conception rates and no
740 effect on the survival, growth, and development to weaning of the offspring.

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

744

745 **Pregnancy:** Pregnancy Category C. There are no adequate and well-controlled studies of
746 TRIZIVIR in pregnant women. Reproduction studies with abacavir, lamivudine, and zidovudine
747 have been performed in animals (see Abacavir, Lamivudine, and Zidovudine sections below).
748 TRIZIVIR should be used during pregnancy only if the potential benefits outweigh the risks.

749 **Abacavir:** Studies in pregnant rats showed that abacavir is transferred to the fetus through
750 the placenta. Fetal malformations (increased incidences of fetal anasarca and skeletal
751 malformations) and developmental toxicity (depressed fetal body weight and reduced
752 crown-rump length) were observed in rats at a dose which produced 35 times the human
753 exposure, based on AUC. Embryonic and fetal toxicities (increased resorptions, decreased fetal
754 body weights) and toxicities to the offspring (increased incidence of stillbirth and lower body
755 weights) occurred at half of the above-mentioned dose in separate fertility studies conducted in
756 rats. In the rabbit, no developmental toxicity and no increases in fetal malformations occurred at
757 doses that produced 8.5 times the human exposure at the recommended dose based on AUC.

758 **Lamivudine:** Studies in pregnant rats and rabbits showed that lamivudine is transferred to
759 the fetus through the placenta. Reproduction studies with orally administered lamivudine have
760 been performed in rats and rabbits at doses up to 4,000 mg/kg/day and 1,000 mg/kg/day,
761 respectively, producing plasma levels up to approximately 35 times that for the adult HIV dose.

762 No evidence of teratogenicity due to lamivudine was observed. Evidence of early
763 embryoletality was seen in the rabbit at exposure levels similar to those observed in humans,
764 but there was no indication of this effect in the rat at exposure levels up to 35 times those in
765 humans.

766 **Zidovudine:** Reproduction studies with orally administered zidovudine in the rat and in the
767 rabbit at doses up to 500 mg/kg/day revealed no evidence of teratogenicity with zidovudine.
768 Zidovudine treatment resulted in embryo/fetal toxicity as evidenced by an increase in the
769 incidence of fetal resorptions in rats given 150 or 450 mg/kg/day and rabbits given
770 500 mg/kg/day. The doses used in the teratology studies resulted in peak zidovudine plasma
771 concentrations (after one half of the daily dose) in rats 66 to 226 times, and in rabbits 12 to
772 87 times, mean steady-state peak human plasma concentrations (after one sixth of the daily dose)
773 achieved with the recommended daily dose (100 mg every 4 hours). In an additional teratology
774 study in rats, a dose of 3,000 mg/kg/day (very near the oral median lethal dose in rats of
775 approximately 3,700 mg/kg) caused marked maternal toxicity and an increase in the incidence of
776 fetal malformations. This dose resulted in peak zidovudine plasma concentrations 350 times peak
777 human plasma concentrations. No evidence of teratogenicity was seen in this experiment at doses
778 of 600 mg/kg/day or less. Two rodent carcinogenicity studies were conducted (see
779 Carcinogenesis, Mutagenesis, and Impairment of Fertility).

780 **Antiretroviral Pregnancy Registry:** To monitor maternal-fetal outcomes of pregnant
781 women exposed to TRIZIVIR or other antiretroviral agents, an Antiretroviral Pregnancy Registry
782 has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

783

784 **Nursing Mothers: The Centers for Disease Control and Prevention recommend that**
785 **HIV-1-infected mothers not breastfeed their infants to avoid risking postnatal transmission**
786 **of HIV-1 infection.**

787 **Abacavir, Lamivudine, and Zidovudine:** Lamivudine and zidovudine are excreted in
788 human breast milk; abacavir and lamivudine are secreted into the milk of lactating rats.

789 Because of both the potential for HIV-1 transmission and the potential for serious adverse
790 reactions in nursing infants, **mothers should be instructed not to breastfeed if they are**
791 **receiving TRIZIVIR.**

792

793 **Pediatric Use:** TRIZIVIR is not intended for use in pediatric patients. TRIZIVIR should not be
794 administered to adolescents who weigh less than 40 kg because it is a fixed-dose tablet that
795 cannot be adjusted for this patient population.

796 **Therapy-Experienced Pediatric Patients:** A randomized, double-blind study,
797 CNA3006, compared ZIAGEN plus lamivudine and zidovudine versus lamivudine and
798 zidovudine in pediatric patients, most of whom were extensively pretreated with nucleoside
799 analogue antiretroviral agents. Patients in this study had a limited response to abacavir.

800

801 **Geriatric Use:** Clinical studies of abacavir, lamivudine, and zidovudine did not include
 802 sufficient numbers of patients aged 65 and over to determine whether they respond differently
 803 from younger patients. In general, dose selection for an elderly patient should be cautious,
 804 reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of
 805 concomitant disease or other drug therapy. TRIZIVIR is not recommended for patients with
 806 impaired renal function (i.e., creatinine clearance <50 mL/min; see PRECAUTIONS: Patients
 807 with Impaired Renal Function and DOSAGE AND ADMINISTRATION).

808 **ADVERSE REACTIONS**

809 **Hypersensitivity Reaction: Serious and sometimes fatal hypersensitivity reactions have**
 810 **been associated with abacavir sulfate, a component of TRIZIVIR (see WARNINGS and**
 811 **PRECAUTIONS: Information for Patients).**

812 Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or
 813 severe) with a $\geq 5\%$ frequency during therapy with abacavir 300 mg twice daily, lamivudine
 814 150 mg twice daily, and zidovudine 300 mg twice daily compared with indinavir 800 mg 3 times
 815 daily, lamivudine 150 mg twice daily, and zidovudine 300 mg twice daily from CNA3005 are
 816 listed in Table 5.

817
 818 **Table 5. Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate**
 819 **Intensity (Grades 2-4, $\geq 5\%$ Frequency) in Therapy-Naive Adults (CNA3005) Through**
 820 **48 Weeks of Treatment**

Adverse Reaction	ZIAGEN plus Lamivudine/Zidovudine (n = 262)	Indinavir plus Lamivudine/Zidovudine (n = 264)
Nausea	19%	17%
Headache	13%	9%
Malaise and fatigue	12%	12%
Nausea and vomiting	10%	10%
Hypersensitivity reaction	8%	2%
Diarrhea	7%	5%
Fever and/or chills	6%	3%
Depressive disorders	6%	4%
Musculoskeletal pain	5%	7%
Skin rashes	5%	4%
Ear/nose/throat infections	5%	4%
Viral respiratory infections	5%	5%
Anxiety	5%	3%
Renal signs/symptoms	<1%	5%
Pain (non-site-specific)	<1%	5%

821

822 Five patients receiving abacavir in study CNA3005 experienced worsening of pre-existing
 823 depression compared to none in the indinavir arm. The background rates of pre-existing
 824 depression were similar in the 2 treatment arms.

825 **Laboratory Abnormalities:** Laboratory abnormalities in study CNA3005 are listed in
 826 Table 6.

827
 828 **Table 6. Treatment-Emergent Laboratory Abnormalities (Grades 3-4) in Study CNA3005**

Grade 3/4 Laboratory Abnormalities	Number of Subjects by Treatment Group	
	ZIAGEN plus Lamivudine/Zidovudine (n = 262)	Indinavir plus Lamivudine/Zidovudine (n = 264)
Elevated CPK (>4 x ULN)	18 (7%)	18 (7%)
ALT (>5.0 x ULN)	16 (6%)	16 (6%)
Neutropenia (<750/mm ³)	13 (5%)	13 (5%)
Hypertriglyceridemia (>750 mg/dL)	5 (2%)	3 (1%)
Hyperamylasemia (>2.0 x ULN)	5 (2%)	1 (<1%)
Hyperglycemia (>13.9 mmol/L)	2 (<1%)	2 (<1%)
Anemia (Hgb ≤6.9 g/dL)	0 (0%)	3 (1%)

829 ULN = Upper limit of normal.
 830 n = Number of patients assessed.

831
 832 **Other Adverse Events:** In addition to adverse reactions in Tables 5 and 6, other adverse
 833 events observed in the expanded access program for abacavir were pancreatitis and increased
 834 GGT.

835
 836 **Observed During Clinical Practice:** The following events have been identified during
 837 post-approval use of abacavir, lamivudine, and/or zidovudine. Because they are reported
 838 voluntarily from a population of unknown size, estimates of frequency cannot be made. These
 839 events have been chosen for inclusion due to a combination of their seriousness, frequency of
 840 reporting, or potential causal connection to lamivudine and/or zidovudine.

841 **Abacavir:**

842 **Cardiovascular:** Myocardial infarction.

843 **Skin:** Suspected Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)
 844 have been reported in patients receiving abacavir primarily in combination with medications
 845 known to be associated with SJS and TEN, respectively. Because of the overlap of clinical signs
 846 and symptoms between hypersensitivity to abacavir and SJS and TEN, and the possibility of
 847 multiple drug sensitivities in some patients, abacavir should be discontinued and not restarted in
 848 such cases.

849 There have also been reports of erythema multiforme with abacavir use.

850 **Abacavir, Lamivudine, and/or Zidovudine:**

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

853 **Cardiovascular:** Cardiomyopathy.

854 **Digestive:** Stomatitis.

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

856 **Gastrointestinal:** Anorexia and/or decreased appetite, abdominal pain, dyspepsia, oral
857 mucosal pigmentation.

858 **General:** Vasculitis, weakness.

859 **Hemic and Lymphatic:** Aplastic anemia, anemia (including pure red cell aplasia and
860 severe anemias progressing on therapy), lymphadenopathy, splenomegaly, thrombocytopenia.

861 **Hepatic and Pancreatic:** Lactic acidosis and hepatic steatosis, elevated bilirubin,
862 elevated transaminases, pancreatitis, posttreatment exacerbation of hepatitis B (see
863 WARNINGS).

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

865 **Musculoskeletal:** Arthralgia, myalgia, muscle weakness, CPK elevation,
866 rhabdomyolysis.

867 **Nervous:** Dizziness, paresthesia, peripheral neuropathy, seizures.

868 **Psychiatric:** Insomnia and other sleep disorders.

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

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

871 OVERDOSAGE

872 **Abacavir:** There is no known antidote for abacavir. It is not known whether abacavir can be
873 removed by peritoneal dialysis or hemodialysis.

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

879 **Zidovudine:** Acute overdoses of zidovudine have been reported in pediatric patients and adults.
880 These involved exposures up to 50 grams. The only consistent findings were nausea and
881 vomiting. Other reported occurrences included headache, dizziness, drowsiness, lethargy, and
882 confusion. Hematologic changes were transient. All patients recovered. Hemodialysis and
883 peritoneal dialysis appear to have a negligible effect on the removal of zidovudine, while
884 elimination of its primary metabolite, GZDV, is enhanced.

885 DOSAGE AND ADMINISTRATION

886 **A Medication Guide and Warning Card that provide information about recognition of**
887 **hypersensitivity reactions should be dispensed with each new prescription and refill.** To
888 facilitate reporting of hypersensitivity reactions and collection of information on each case, an

889 Abacavir Hypersensitivity Registry has been established. Physicians should register patients by
890 calling 1-800-270-0425.

891 The recommended oral dose of TRIZIVIR for adults and adolescents is 1 tablet twice daily.
892 TRIZIVIR is not recommended in adolescents who weigh less than 40 kg because it is a
893 fixed-dose tablet.

894 **Dose Adjustment:** Because it is a fixed-dose tablet, TRIZIVIR should not be prescribed for
895 patients requiring dosage adjustment such as those with creatinine clearance <50 mL/min,
896 patients with hepatic impairment, or patients experiencing dose-limiting adverse events.

897 HOW SUPPLIED

898 TRIZIVIR is available as tablets. Each tablet contains 300 mg of abacavir as abacavir sulfate,
899 150 mg of lamivudine, and 300 mg of zidovudine. The tablets are blue-green capsule-shaped,
900 film-coated, and imprinted with GX LL1 on one side with no markings on the reverse side. They
901 are packaged as follows:

902 Bottles of 60 Tablets (NDC 0173-0691-00).

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

905 ANIMAL TOXICOLOGY

906 Myocardial degeneration was found in mice and rats following administration of abacavir for
907 2 years. The systemic exposures were equivalent to 7 to 24 times the expected systemic exposure
908 in humans. The clinical relevance of this finding has not been determined.

909 REFERENCE

910 1. Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study Group. *Lancet*.
911 2008;371 (9622):1417-1426.

912

913 Revised March 2009

914

915 MEDICATION GUIDE

916

917 TRIZIVIR® (TRY-zih-veer) Tablets

918

919 **Generic name:** abacavir (uh-BACK-ah-veer) sulfate, lamivudine (la-MIV-yoo-deen), and
920 zidovudine (zahy-doh-vyoo-deen)

921

922 Read the Medication Guide that comes with TRIZIVIR before you start taking it and each time
923 you get a refill because there may be new information. This information does not take the place
924 of talking to your doctor about your medical condition or your treatment. Be sure to carry your
925 TRIZIVIR Warning Card with you at all times.

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

- **Serious Allergic Reaction to Abacavir.** TRIZIVIR contains abacavir (also contained in ZIAGEN® and EPZICOM®). Patients taking TRIZIVIR may have a serious allergic reaction (hypersensitivity reaction) that can cause death. **Your risk of this allergic reaction is much higher if you have a gene variation called HLA-B*5701 than if you do not. Your doctor can determine with a blood test if you have this gene variation. If you get a symptom from 2 or more of the following groups while taking TRIZIVIR, call your doctor right away to determine if you should stop taking this medicine.**

	Symptom(s)
Group 1	Fever
Group 2	Rash
Group 3	Nausea, vomiting, diarrhea, abdominal (stomach area) pain
Group 4	Generally ill feeling, extreme tiredness, or achiness
Group 5	Shortness of breath, cough, sore throat

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A list of these symptoms is on the Warning Card your pharmacist gives you. Carry this Warning Card with you.

If you stop TRIZIVIR because of an allergic reaction, NEVER take TRIZIVIR (abacavir sulfate, lamivudine, and zidovudine) or any other abacavir-containing medicine (ZIAGEN, EPZICOM) again. If you take TRIZIVIR or any other abacavir-containing medicine again after you have had an allergic reaction, WITHIN HOURS you may get life-threatening symptoms that may include very low blood pressure or death.

If you stop TRIZIVIR, for any other reason, even for a few days, and you are not allergic to TRIZIVIR, talk with your doctor before taking it again. Taking TRIZIVIR again can cause a serious or life-threatening reaction, even if you never had an allergic reaction to it before. If your doctor tells you that you can take TRIZIVIR again, start taking it when you are around medical help or people who can call a doctor if you need one.

- **Blood problems.** RETROVIR®, one of the medicines in TRIZIVIR, can cause serious blood cell problems. These include reduced numbers of white blood cells (neutropenia) and extremely reduced numbers of red blood cells (anemia). These blood cell problems are especially likely to happen in patients with advanced human immunodeficiency virus (HIV) disease or AIDS. Your doctor should be checking your blood cell counts regularly while you

959 are taking TRIZIVIR. This is especially important if you have advanced HIV or AIDS. This
960 is to make sure that any blood cell problems are found quickly.

- 961 • **Lactic Acidosis. Some HIV medicines, including TRIZIVIR, can cause a rare but**
962 **serious condition called lactic acidosis with liver enlargement (hepatomegaly).** Nausea
963 and tiredness that don't get better may be symptoms of lactic acidosis. In some cases this
964 condition can cause death. Women, overweight people, and people who have taken HIV
965 medicines like TRIZIVIR for a long time have a higher chance of getting lactic acidosis and
966 liver enlargement. Lactic acidosis is a medical emergency and must be treated in the hospital.
- 967 • **Worsening of hepatitis B virus (HBV) infection.** Patients with HBV infection who take
968 TRIZIVIR and then stop it, may get “flare-ups” of their hepatitis. “Flare-up” is when the
969 disease suddenly returns in a worse way than before. If you have HBV infection, your doctor
970 should closely monitor your liver function for several months after stopping TRIZIVIR. You
971 may need to take anti-HBV medicines.
- 972 • **Muscle weakness (myopathy).** RETROVIR, one of the medicines in TRIZIVIR, can cause
973 muscle weakness. This can be a serious problem.
- 974 • **Use with interferon- and ribavirin-based regimens.** Worsening of liver disease
975 (sometimes resulting in death) has occurred in patients infected with both HIV and hepatitis
976 C virus who are taking anti-HIV medicines and are also being treated for hepatitis C with
977 interferon with or without ribavirin. If you are taking TRIZIVIR as well as interferon with or
978 without ribavirin and you experience side effects, be sure to tell your doctor.

979
980 TRIZIVIR can have other serious side effects. Be sure to read the section below entitled "What
981 are the possible side effects of TRIZIVIR?"

982

983 **What is TRIZIVIR?**

984 TRIZIVIR is a prescription medicine used to treat HIV infection. TRIZIVIR includes
985 3 medicines: ZIAGEN (abacavir), EPIVIR[®] (lamivudine or 3TC), and RETROVIR[®]
986 (zidovudine, AZT, or ZDV). See the end of this Medication Guide for a complete list of
987 ingredients in TRIZIVIR. All 3 of these medicines are called nucleoside analogue reverse
988 transcriptase inhibitors (NRTIs). When used together, they help lower the amount of HIV in your
989 blood. This helps to keep your immune system as healthy as possible so it can fight infection.

990

991 Different combinations of medicines are used to treat HIV infection. You and your doctor should
992 discuss which combination of medicines is best for you.

993

- 994 • **TRIZIVIR does not cure HIV infection or AIDS.** We do not know if TRIZIVIR will help
995 you live longer or have fewer of the medical problems that people get with HIV or AIDS. It
996 is very important that you see your doctor regularly while you are taking TRIZIVIR.
- 997 • **TRIZIVIR does not lower the risk of passing HIV to other people through sexual**
998 **contact, sharing needles, or being exposed to your blood.** For your health and the health of

999 others, it is important to always practice safe sex by using a latex or polyurethane condom or
1000 other barrier method to lower the chance of sexual contact with semen, vaginal secretions, or
1001 blood. Never use or share dirty needles.

1002

1003 **Who should not take TRIZIVIR?**

1004 **Do not take TRIZIVIR if you:**

- 1005 • **have ever had a serious allergic reaction (a hypersensitivity reaction) to TRIZIVIR or**
- 1006 **any other medicine (ZIAGEN, EPZICOM) that has abacavir as an ingredient. See the**
- 1007 **end of this Medication Guide for a complete list of ingredients in TRIZIVIR.**
- 1008 • **have a liver that does not function properly**
- 1009 • **are an adolescent who weighs less than 90 pounds.**

1010

1011 **Before starting TRIZIVIR, tell your doctor about all your medical problems, including if**
1012 **you:**

- 1013 • **have been tested and know whether or not you have a particular gene variation called**
1014 **HLA-B*5701.**
- 1015 • **are pregnant or planning to become pregnant.** We do not know if TRIZIVIR will harm
1016 your unborn child. You and your doctor will need to decide if TRIZIVIR is right for you. If
1017 you use TRIZIVIR while you are pregnant, talk to your doctor about how you can be on the
1018 Antiviral Pregnancy Registry for TRIZIVIR.
- 1019 • **are breastfeeding.** Some of the ingredients in TRIZIVIR can be passed to your baby in your
1020 breast milk. It is not known if they could harm your baby. Also, mothers with HIV should not
1021 breastfeed because HIV can be passed to the baby in the breast milk.
- 1022 • **have liver problems including hepatitis B virus infection.**
- 1023 • **have kidney problems.**
- 1024 • **have low blood cell counts (bone marrow problem).** Ask your doctor if you are not sure.
- 1025 • **have heart problems, smoke, or suffer from diseases that increase your risk of heart**
1026 **disease such as high blood pressure, high cholesterol, or diabetes.**

1027

1028 **Tell your doctor about all the medicines you take, including prescription and**
1029 **nonprescription medicines, vitamins, and herbal supplements. Especially tell your doctor if**
1030 **you take any of the following medicines*:**

- 1031 • **methadone**
- 1032 • **trimethoprim (TMP/sulfamethoxazole [SMX] [BACTRIM[®], SEPTRA[®]])**
- 1033 • **ganciclovir (CYTOVENE[®], DHPG)**
- 1034 • **interferon-alfa**
- 1035 • **doxorubicin (ADRIAMYCIN[®])**
- 1036 • **ribavirin (COPEGUS[®], REBETOL[®], VIRAZOLE[®])**
- 1037 • **any bone marrow suppressive medicines or cytotoxic medicines.** Ask your doctor if you
1038 are not sure.

- 1039 • **any of the following anti-HIV medicines: COMBIVIR[®]** (lamivudine and zidovudine),
1040 **EMTRIVIA[®]** (emtricitabine), **EPIVIR or EPIVIR-HBV[®]** (lamivudine, 3TC), **EPZICOM**
1041 (abacavir sulfate and lamivudine), **HIVID[®]** (zalcitabine, ddC), **RETROVIR** (zidovudine,
1042 AZT, or ZDV), **TRUVADA[®]** (emtricitabine and tenofovir), **ZERIT[®]** (stavudine, d4T), or
1043 **ZIAGEN** (abacavir sulfate).

1044

1045 **How should I take TRIZIVIR?**

1046 **Take TRIZIVIR by mouth exactly as your doctor prescribes it.** The usual dosage is 1 tablet
1047 twice a day. Do not skip doses.

- 1048 • **You can take TRIZIVIR with or without food.**
- 1049 • **If you miss a dose of TRIZIVIR, take the missed dose right away. Then, take the next**
1050 **dose at the usual scheduled time.**
- 1051 • **Do not let your TRIZIVIR run out.** If you stop your anti-HIV medicines, even for a short
1052 time, the amount of virus in your blood may increase and the virus may become harder to
1053 treat.
- 1054 • **Starting TRIZIVIR again can cause a serious allergic reaction or life-threatening**
1055 **reaction, even if you have never had an allergic reaction to it before.** If you run out of
1056 TRIZIVIR even for a few days, you must ask your doctor if you can start TRIZIVIR again. If
1057 your doctor tells you that you can take TRIZIVIR again, start taking it when you are around
1058 medical help or people who can call a doctor if you need one.
- 1059 • **If you take too much TRIZIVIR, call your doctor or poison control center right away.**

1060

1061 **What should I avoid while taking TRIZIVIR?**

1062 Do not take COMBIVIR (**lamivudine and zidovudine**), EPIVIR (**lamivudine, 3TC**),
1063 EPZICOM (**abacavir sulfate and lamivudine**), RETROVIR (**zidovudine, AZT, or ZDV**), or
1064 ZIAGEN (**abacavir sulfate**) while taking TRIZIVIR. These medicines are already in TRIZIVIR.

1065

1066 **Avoid doing things that can spread HIV infection,** as TRIZIVIR does not stop you from
1067 passing the HIV infection to others.

- 1068 • **Do not share needles or other injection equipment.**
- 1069 • **Do not share personal items that can have blood or body fluids on them, like**
1070 **toothbrushes and razor blades.**
- 1071 • **Do not have any kind of sex without protection.** Always practice safe sex by using a latex
1072 or polyurethane condom or other barrier method to lower the chance of sexual contact with
1073 semen, vaginal secretions, or blood.
- 1074 • **Do not breastfeed.** Some of the medicines in TRIZIVIR can be passed to babies in breast
1075 milk and could harm the baby. Also, mothers with HIV should not breastfeed because HIV
1076 can be passed to the baby in the breast milk.

1077

1078 **What are the possible side effects of TRIZIVIR?**

- 1079 **TRIZIVIR can cause the following serious side effects.** See "What is the most important
1080 information I should know about TRIZIVIR?" at the beginning of this Medication Guide.
- 1081 • **Serious allergic reaction that can cause death.**
 - 1082 • **Lactic acidosis with liver enlargement (hepatomegaly) that can cause death.**
 - 1083 • **Worsening of HBV infection.** (See "What is the most important information I should know
1084 about TRIZIVIR?" at the beginning of this Medication Guide.)
 - 1085 • **Blood problems.**
 - 1086 • **Muscle weakness.**
 - 1087 • **Changes in immune system.** When you start taking HIV medicines, your immune system
1088 may get stronger and could begin to fight infections that have been hidden in your body, such
1089 as pneumonia, herpes virus, or tuberculosis. If you have new symptoms after starting your
1090 HIV medicines, be sure to tell your doctor.
 - 1091 • **Changes in body fat.** These changes have happened in patients taking antiretroviral
1092 medicines like TRIZIVIR. The changes may include an increased amount of fat in the upper
1093 back and neck ("buffalo hump"), breast, and around the back, chest, and stomach area. Loss
1094 of fat from the legs, arms, and face may also happen. The cause and long-term health effects
1095 of these conditions are not known.

1096

1097 Some HIV medicines including TRIZIVIR may increase your risk of heart attack. If you have
1098 heart problems, smoke, or suffer from diseases that increase your risk of heart disease such as
1099 high blood pressure, high cholesterol, or diabetes, tell your doctor.

1100

1101 The most common adverse events ($\geq 5\%$) of at least moderate intensity associated with the use of
1102 TRIZIVIR include nausea, headache, weakness or tiredness, vomiting, hypersensitivity reaction,
1103 diarrhea, fever and/or chills, depression, muscle and joint pain, skin rashes, ear/nose/throat
1104 infections, cold symptoms, and nervousness.

1105

1106 This list of side effects is not complete. Call your doctor for medical advice about side effects.
1107 You may report side effects to FDA at 1-800-FDA-1088.

1108

1109 **How should I store TRIZIVIR?**

- 1110 • Store TRIZIVIR between 59° to 86°F (15° to 30°C).
- 1111 • **Keep TRIZIVIR and all medicines out of the reach of children.**

1112

1113 **General information for safe and effective use of TRIZIVIR**

1114 Medicines are sometimes prescribed for conditions that are not mentioned in Medication Guides.
1115 Do not use TRIZIVIR for a condition for which it was not prescribed. Do not give TRIZIVIR to
1116 other people, even if they have the same symptoms that you have. It may harm them.

1117

1118 This Medication Guide summarizes the most important information about TRIZIVIR. If you
1119 would like more information, talk with your doctor. You can ask your doctor or pharmacist for
1120 the information that is written for healthcare professionals or call 1-888-825-5249.

1121

1122 **What are the ingredients in TRIZIVIR?**

1123 **Active ingredients:** abacavir sulfate, lamivudine, and zidovudine

1124 **Inactive ingredients:** Each film-coated TRIZIVIR Tablet contains the inactive ingredients
1125 magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The tablets are
1126 coated with a film (OPADRY® green 03B11434) that is made of FD&C Blue No. 2,
1127 hypromellose, polyethylene glycol, titanium dioxide, and yellow iron oxide.

1128

1129 *This Medication Guide has been approved by the US Food and Drug Administration.*

1130

1131

1132

1133 COMBIVIR, EPIVIR, EPZICOM, RETROVIR, TRIZIVIR, and ZIAGEN are registered
1134 trademarks of GlaxoSmithKline.

1135

1136 * The brands listed are trademarks of their respective owners and are not trademarks of
1137 GlaxoSmithKline. The makers of these brands are not affiliated with and do not endorse
1138 GlaxoSmithKline or its products.

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1142 Research Triangle Park, NC 27709

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1144 Lamivudine is manufactured under agreement from

1145 **Shire Pharmaceuticals Group plc**

1146 Basingstoke, UK

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1151 TRZ:xPI

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