

## **PRESCRIBING INFORMATION**

EPZICOM®

**(abacavir sulfate and lamivudine)  
Tablets**

## **WARNINGS**

**EPZICOM** contains 2 nucleoside analogues (abacavir sulfate and lamivudine) and is intended only for patients whose regimen would otherwise include these 2 components.

**Hypersensitivity Reactions:** Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir sulfate, a component of EPZICOM. 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 EPZICOM as soon as a hypersensitivity reaction is suspected.**

**P**atients 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 EPZICOM if hypersensitivity cannot be ruled out, even when other diagnoses are possible**

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

**Reintroduction of EPZICOM 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).**

**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, 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 human immunodeficiency virus (HIV-1) and have discontinued lamivudine, which is one

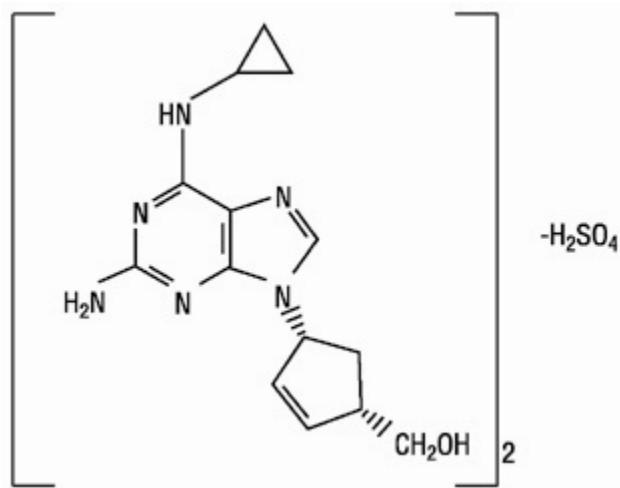
39 component of EPZICOM. Hepatic function should be monitored closely with both clinical  
40 and laboratory follow-up for at least several months in patients who discontinue  
41 EPZICOM and are co-infected with HIV-1 and HBV. If appropriate, initiation of  
42 anti-hepatitis B therapy may be warranted (see WARNINGS).

43 **DESCRIPTION**

44 **EPZICOM:** EPZICOM Tablets contain the following 2 synthetic nucleoside analogues: abacavir  
45 sulfate (ZIAGEN®, also a component of TRIZIVIR®) and lamivudine (also known as EPIVIR®  
46 or 3TC) with inhibitory activity against HIV-1.

47 EPZICOM Tablets are for oral administration. Each orange, film-coated tablet contains the  
48 active ingredients 600 mg of abacavir as abacavir sulfate and 300 mg of lamivudine, and the  
49 inactive ingredients magnesium stearate, microcrystalline cellulose, and sodium starch glycolate.  
50 The tablets are coated with a film (Opadry® orange YS-1-13065-A) that is made of FD&C  
51 Yellow No. 6, hypromellose, polyethylene glycol 400, polysorbate 80, and titanium dioxide.

52 **Abacavir Sulfate:** The chemical name of abacavir sulfate is (1*S,cis*)-4-[2-amino-6-  
53 (cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1). Abacavir  
54 sulfate is the enantiomer with *IS, 4R* absolute configuration on the cyclopentene ring. It has a  
55 molecular formula of  $(\text{C}_{14}\text{H}_{18}\text{N}_6\text{O})_2 \cdot \text{H}_2\text{SO}_4$  and a molecular weight of 670.76 daltons. It has the  
56 following structural formula:  
57

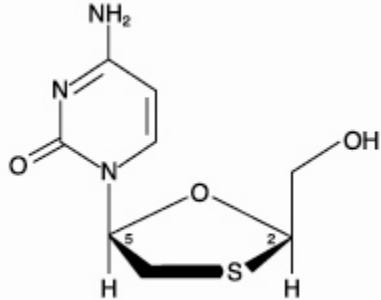


58  
59  
60 Abacavir sulfate is a white to off-white solid with a solubility of approximately 77 mg/mL in  
61 distilled water at 25°C.

62 In vivo, abacavir sulfate dissociates to its free base, abacavir. All dosages for abacavir sulfate  
63 are expressed in terms of abacavir.

64 **Lamivudine:** The chemical name of lamivudine is (2*R,cis*)-4-amino-1-(2-hydroxymethyl-1,3-  
65 oxathiolan-5-yl)-(1*H*)-pyrimidin-2-one. Lamivudine is the (-)enantiomer of a dideoxy analogue  
66 of cytidine. Lamivudine has also been referred to as (-)2',3'-dideoxy, 3'-thiacytidine. It has a

67 molecular formula of C<sub>8</sub>H<sub>11</sub>N<sub>3</sub>O<sub>3</sub>S and a molecular weight of 229.3 daltons. It has the following  
68 structural formula:



69  
70 Lamivudine is a white to off-white crystalline solid with a solubility of approximately  
71 70 mg/mL in water at 20°C.

## 72 MICROBIOLOGY

73 **Mechanism of Action:** Abacavir is a carbocyclic synthetic nucleoside analogue. Abacavir is  
74 converted by cellular enzymes to the active metabolite, carbovir triphosphate (CBV-TP), an  
75 analogue of deoxyguanosine-5'-triphosphate (dGTP). CBV-TP inhibits the activity of HIV-1  
76 reverse transcriptase (RT) both by competing with the natural substrate dGTP and by its  
77 incorporation into viral DNA. The lack of a 3'-OH group in the incorporated nucleotide analogue  
78 prevents the formation of the 5' to 3' phosphodiester linkage essential for DNA chain elongation,  
79 and therefore, the viral DNA growth is terminated. CBV-TP is a weak inhibitor of cellular DNA  
80 polymerases  $\alpha$ ,  $\beta$ , and  $\gamma$ .

81 Lamivudine is a synthetic nucleoside analogue. Intracellularly lamivudine is phosphorylated  
82 to its active 5'-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode  
83 of action of 3TC-TP is inhibition of RT via DNA chain termination after incorporation of the  
84 nucleotide analogue. CBV-TP and 3TC-TP are weak inhibitors of cellular DNA polymerases  $\alpha$ ,  
85  $\beta$ , and  $\gamma$ .

86 **Antiviral Activity: Abacavir:** The antiviral activity of abacavir against HIV-1 was evaluated  
87 against a T-cell tropic laboratory strain HIV-1<sub>IIIB</sub> in lymphoblastic cell lines, a  
88 monocyte/macrophage tropic laboratory strain HIV-1<sub>BaL</sub> in primary monocytes/macrophages,  
89 and clinical isolates in peripheral blood mononuclear cells. The concentration of drug necessary  
90 to effect viral replication by 50 percent (EC<sub>50</sub>) ranged from 3.7 to 5.8  $\mu$ M (1  $\mu$ M = 0.28 mcg/mL)  
91 and 0.07 to 1.0  $\mu$ M against HIV-1<sub>IIIB</sub> and HIV-1<sub>BaL</sub>, respectively, and was 0.26  $\pm$  0.18  $\mu$ M  
92 against 8 clinical isolates. The EC<sub>50</sub> values of abacavir against different HIV-1 clades (A-G)  
93 ranged from 0.0015 to 1.05  $\mu$ M, and against HIV-2 isolates, from 0.024 to 0.49  $\mu$ M. Ribavirin  
94 (50  $\mu$ M) had no effect on the anti-HIV-1 activity of abacavir in cell culture.

95 **Lamivudine:** The antiviral activity of lamivudine against HIV-1 was assessed in a number of  
96 cell lines (including monocytes and fresh human peripheral blood lymphocytes) using standard

97 susceptibility assays. EC<sub>50</sub> values were in the range of 0.003 to 15 µM (1 µM = 0.23 mcg/mL).  
98 HIV-1 from therapy-naive subjects with no amino acid substitutions associated with resistance  
99 gave median EC<sub>50</sub> values of 0.429 µM (range: 0.200 to 2.007 µM) from Virco (n = 92 baseline  
100 samples from COLA40263) and 2.35 µM (1.37 to 3.68 µM) from Monogram Biosciences  
101 (n = 135 baseline samples from ESS30009). The EC<sub>50</sub> values of lamivudine against different  
102 HIV-1 clades (A-G) ranged from 0.001 to 0.120 µM, and against HIV-2 isolates from 0.003 to  
103 0.120 µM in peripheral blood mononuclear cells. Ribavirin (50 µM) decreased the anti-HIV-1  
104 activity of lamivudine by 3.5 fold in MT-4 cells.

105 The combination of abacavir and lamivudine has demonstrated antiviral activity in cell culture  
106 against non-subtype B isolates and HIV-2 isolates with equivalent antiviral activity as for  
107 subtype B isolates. Abacavir/lamivudine had additive to synergistic activity in cell culture in  
108 combination with the nucleoside reverse transcriptase inhibitors (NRTIs) emtricitabine,  
109 stavudine, tenofovir, zalcitabine, zidovudine; the non-nucleoside reverse transcriptase inhibitors  
110 (NNRTIs) delavirdine, efavirenz, nevirapine; the protease inhibitors (PIs) amprenavir, indinavir,  
111 lopinavir, nelfinavir, ritonavir, saquinavir; or the fusion inhibitor, enfuvirtide. Ribavirin, used in  
112 combination with interferon for the treatment of HCV infection, decreased the anti-HIV-1  
113 potency of abacavir/lamivudine reproducibly by 2- to 6-fold in cell culture.

114 **Resistance:** HIV-1 isolates with reduced susceptibility to the combination of abacavir and  
115 lamivudine have been selected in cell culture and have also been obtained from patients failing  
116 abacavir/lamivudine-containing regimens. Genotypic characterization of  
117 abacavir/lamivudine-resistant viruses selected in cell culture identified amino acid substitutions  
118 M184V/I, K65R, L74V, and Y115F in HIV-1 RT.

119 Genotypic analysis of isolates selected in cell culture and recovered from abacavir-treated  
120 patients demonstrated that amino acid substitutions K65R, L74V, Y115F, and M184V/I in  
121 HIV-1 RT contributed to abacavir resistance. Genotypic analysis of isolates selected in cell  
122 culture and recovered from lamivudine-treated patients showed that the resistance was due to a  
123 specific amino acid substitution in HIV-1 RT at codon 184 changing the methionine to either  
124 isoleucine or valine (M184V/I). In a study of therapy-naive adults receiving ZIAGEN 600 mg  
125 once daily (n = 384) or 300 mg twice daily (n = 386) in a background regimen of lamivudine  
126 300 mg and efavirenz 600 mg once daily (Study CNA30021), the incidence of virologic failure  
127 at 48 weeks was similar between the 2 groups (11% in both arms). Genotypic (n = 38) and  
128 phenotypic analyses (n = 35) of virologic failure isolates from this study showed that the RT  
129 substitutions that emerged during abacavir/lamivudine once-daily and twice-daily therapy were  
130 K65R, L74V, Y115F, and M184V/I. The abacavir- and lamivudine-associated resistance  
131 substitution M184V/I was the most commonly observed substitution in virologic failure isolates  
132 from patients receiving abacavir/lamivudine once daily (56%, 10/18) and twice daily (40%,  
133 8/20).

134 Thirty-nine percent (7/18) of the isolates from patients who experienced virologic failure in  
135 the abacavir once-daily arm had a >2.5-fold decrease in abacavir susceptibility with a  
136 median-fold decrease of 1.3 (range: 0.5 to 11) compared with 29% (5/17) of the failure isolates

137 in the twice-daily arm with a median-fold decrease of 0.92 (range: 0.7 to 13). Fifty-six percent  
138 (10/18) of the virologic failure isolates in the once-daily abacavir group compared with 41%  
139 (7/17) of the failure isolates in the twice-daily abacavir group had a >2.5-fold decrease in  
140 lamivudine susceptibility with median-fold changes of 81 (range 0.79 to >116) and 1.1 (range  
141 0.68 to >116) in the once-daily and twice-daily abacavir arms, respectively.

142 **Cross-Resistance:** Cross-resistance has been observed among NRTIs. Viruses containing  
143 abacavir and lamivudine resistance-associated amino acid substitutions, namely, K65R, L74V,  
144 M184V, and Y115F, exhibit cross-resistance to didanosine, emtricitabine, lamivudine, tenofovir,  
145 and zalcitabine in cell culture and in patients. The K65R substitution can confer resistance to  
146 abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine; the L74V  
147 substitution can confer resistance to abacavir, didanosine, and zalcitabine; and the M184V  
148 substitution can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, and  
149 zalcitabine.

150 The combination of abacavir/lamivudine has demonstrated decreased susceptibility to viruses  
151 with the substitutions K65R with or without the M184V/I substitution, viruses with L74V plus  
152 the M184V/I substitution, and viruses with thymidine analog mutations (TAMs: M41L, D67N,  
153 K70R, L210W, T215Y/F, K219 E/R/H/Q/N) plus M184V. An increasing number of TAMs is  
154 associated with a progressive reduction in abacavir susceptibility.

## 155 **CLINICAL PHARMACOLOGY**

156 **Pharmacokinetics in Adults: EPZICOM:** In a single-dose, 3-way crossover bioavailability  
157 study of 1 EPZICOM Tablet versus 2 ZIAGEN Tablets (2 x 300 mg) and 2 EPIVIR Tablets (2 x  
158 150 mg) administered simultaneously in healthy subjects (n = 25), there was no difference in the  
159 extent of absorption, as measured by the area under the plasma concentration-time curve (AUC)  
160 and maximal peak concentration ( $C_{max}$ ), of each component.

161 **Abacavir:** Following oral administration, abacavir is rapidly absorbed and extensively  
162 distributed. After oral administration of a single dose of 600 mg of abacavir in 20 patients,  $C_{max}$   
163 was  $4.26 \pm 1.19$  mcg/mL (mean  $\pm$  SD) and  $AUC_{\infty}$  was  $11.95 \pm 2.51$  mcg•hr/mL. Binding of  
164 abacavir to human plasma proteins is approximately 50% and was independent of concentration.  
165 Total blood and plasma drug-related radioactivity concentrations are identical, demonstrating  
166 that abacavir readily distributes into erythrocytes. The primary routes of elimination of abacavir  
167 are metabolism by alcohol dehydrogenase to form the 5'-carboxylic acid and glucuronyl  
168 transferase to form the 5'-glucuronide.

169 **Lamivudine:** Following oral administration, lamivudine is rapidly absorbed and extensively  
170 distributed. After multiple-dose oral administration of lamivudine 300 mg once daily for 7 days  
171 to 60 healthy volunteers, steady-state  $C_{max}$  ( $C_{max,ss}$ ) was  $2.04 \pm 0.54$  mcg/mL (mean  $\pm$  SD) and  
172 the 24-hour steady-state AUC ( $AUC_{24,ss}$ ) was  $8.87 \pm 1.83$  mcg•hr/mL. Binding to plasma protein  
173 is low. Approximately 70% of an intravenous dose of lamivudine is recovered as unchanged  
174 drug in the urine. Metabolism of lamivudine is a minor route of elimination. In humans, the only

175 known metabolite is the trans-sulfoxide metabolite (approximately 5% of an oral dose after  
176 12 hours).

177 The steady-state pharmacokinetic properties of the EPIVIR 300-mg Tablet once daily for  
178 7 days compared with the EPIVIR 150-mg Tablet twice daily for 7 days were assessed in a  
179 crossover study in 60 healthy volunteers. EPIVIR 300 mg once daily resulted in lamivudine  
180 exposures that were similar to EPIVIR 150 mg twice daily with respect to plasma AUC<sub>24,ss</sub>;  
181 however, C<sub>max,ss</sub> was 66% higher and the trough value was 53% lower compared with the  
182 150-mg twice-daily regimen. Intracellular lamivudine triphosphate exposures in peripheral blood  
183 mononuclear cells were also similar with respect to AUC<sub>24,ss</sub> and C<sub>max,ss</sub>; however, trough  
184 values were lower compared with the 150-mg twice-daily regimen. Inter-subject variability was  
185 greater for intracellular lamivudine triphosphate concentrations versus lamivudine plasma trough  
186 concentrations. The clinical significance of observed differences for both plasma lamivudine  
187 concentrations and intracellular lamivudine triphosphate concentrations is not known.

188 In humans, abacavir and lamivudine are not significantly metabolized by cytochrome P450  
189 enzymes.

190 The pharmacokinetic properties of abacavir and lamivudine in fasting patients are summarized  
191 in Table 1.

192  
193 **Table 1. Pharmacokinetic Parameters\* for Abacavir and Lamivudine in Adults**

Parameter	Abacavir		Lamivudine	
Oral bioavailability (%)	86 ± 25	n = 6	86 ± 16	n = 12
Apparent volume of distribution (L/kg)	0.86 ± 0.15	n = 6	1.3 ± 0.4	n = 20
Systemic clearance (L/hr/kg)	0.80 ± 0.24	n = 6	0.33 ± 0.06	n = 20
Renal clearance (L/hr/kg)	.007 ± .008	n = 6	0.22 ± 0.06	n = 20
Elimination half-life (hr)	1.45 ± 0.32	n = 20	5 to 7 <sup>†</sup>	

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

195 <sup>†</sup>Approximate range.

196  
197 **Effect of Food on Absorption of EPZICOM:** EPZICOM may be administered with or  
198 without food. Administration with a high-fat meal in a single-dose bioavailability study resulted  
199 in no change in AUC<sub>last</sub>, AUC<sub>∞</sub>, and C<sub>max</sub> for lamivudine. Food did not alter the extent of  
200 systemic exposure to abacavir (AUC<sub>∞</sub>), but the rate of absorption (C<sub>max</sub>) was decreased  
201 approximately 24% compared with fasted conditions (n = 25). These results are similar to those  
202 from previous studies of the effect of food on abacavir and lamivudine tablets administered  
203 separately.

204 **Special Populations: Impaired Renal Function:**

205 **EPZICOM:** Because lamivudine requires dose adjustment in the presence of renal  
206 insufficiency, EPZICOM is not recommended for use in patients with creatinine clearance  
207 <50 mL/min (see PRECAUTIONS).

208      **Impaired Hepatic Function: EPZICOM:** Abacavir is contraindicated in patients with  
209      moderate to severe hepatic impairment and dose reduction is required in patients with mild  
210      hepatic impairment. Because EPZICOM is a fixed-dose combination and cannot be dose  
211      adjusted, EPZICOM is contraindicated for patients with hepatic impairment.

212      **Pregnancy:** See PRECAUTIONS: Pregnancy.

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

215      **Nursing Mothers:** See PRECAUTIONS: Nursing Mothers.

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

217      **Lamivudine:** Samples of breast milk obtained from 20 mothers receiving lamivudine  
218      monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice daily and  
219      300 mg zidovudine twice daily) had measurable concentrations of lamivudine.

220      **Pediatric Patients: EPZICOM:** The pharmacokinetics of EPZICOM in pediatric patients  
221      are under investigation. There are insufficient data at this time to recommend a dose (see  
222      PRECAUTIONS: Pediatric Use).

223      **Geriatric Patients:** The pharmacokinetics of abacavir and lamivudine have not been studied  
224      in patients over 65 years of age.

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

228      **Lamivudine:** A pharmacokinetic study in healthy male (n = 12) and female (n = 12)  
229      subjects showed no gender differences in lamivudine AUC<sub>∞</sub> normalized for body weight.

230      **Race: Abacavir:** There are no significant differences between blacks and Caucasians in  
231      abacavir pharmacokinetics.

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

233      **Drug Interactions:** See PRECAUTIONS: Drug Interactions. The drug interactions described  
234      are based on studies conducted with the individual nucleoside analogues. In humans, abacavir  
235      and lamivudine are not significantly metabolized by cytochrome P450 enzymes nor do they  
236      inhibit or induce this enzyme system; therefore, it is unlikely that clinically significant drug  
237      interactions will occur with drugs metabolized through these pathways.

238      **Abacavir:** Fifteen HIV-1-infected patients were enrolled in a crossover-designed drug  
239      interaction study evaluating single doses of abacavir (600 mg), lamivudine (150 mg), and  
240      zidovudine (300 mg) alone or in combination. Analysis showed no clinically relevant changes in  
241      the pharmacokinetics of abacavir with the addition of lamivudine or zidovudine or the  
242      combination of lamivudine and zidovudine. Lamivudine exposure (AUC decreased 15%) and  
243      zidovudine exposure (AUC increased 10%) did not show clinically relevant changes with  
244      concurrent abacavir.

245      In a study of 11 HIV-1-infected patients receiving methadone-maintenance therapy (40 mg  
246      and 90 mg daily), with 600 mg of ZIAGEN twice daily (twice the currently recommended dose),  
247      oral methadone clearance increased 22% (90% CI: 6% to 42%). This alteration will not result in

248 a methadone dose modification in the majority of patients; however, an increased methadone  
249 dose may be required in a small number of patients.

250 **Lamivudine:** No clinically significant alterations in lamivudine or zidovudine  
251 pharmacokinetics were observed in 12 asymptomatic HIV-1-infected adult patients given a  
252 single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg q  
253 12 hr). Lamivudine pharmacokinetics are not significantly affected by abacavir.  
254

255 **Table 2. Effect of Coadministered Drugs on Abacavir and Lamivudine AUC\***

**Note: ROUTINE DOSE MODIFICATION OF ABACAVIR AND LAMIVUDINE IS NOT  
WARRANTED WITH COADMINISTRATION OF THE FOLLOWING DRUGS.**

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%	↔
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%	↔

256 ↑ = Increase; ↔ = no significant change; AUC = area under the concentration versus time curve;  
257 CI = confidence interval.

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

259

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

266 **INDICATIONS AND USAGE**

267 EPZICOM Tablets, in combination with other antiretroviral agents, are indicated for the  
268 treatment of HIV-1 infection.

269 Additional important information on the use of EPZICOM for treatment of HIV-1 infection:

- 270 • EPZICOM is one of multiple products containing abacavir. Before starting EPZICOM, review  
271 medical history for prior exposure to any abacavir-containing product in order to avoid  
272 reintroduction in a patient with a history of hypersensitivity to abacavir.  
273 • In one controlled study (CNA30021), more patients taking ZIAGEN 600 mg once daily had  
274 severe hypersensitivity reactions compared with patients taking ZIAGEN 300 mg twice daily.  
275 • As part of a triple-drug regimen, EPZICOM Tablets are recommended for use with  
276 antiretroviral agents from different pharmacological classes and not with other  
277 nucleoside/nucleotide reverse transcriptase inhibitors.

278 See WARNINGS, ADVERSE REACTIONS, and Description of Clinical Studies.

279 **Description of Clinical Studies: EPZICOM:** There have been no clinical trials conducted  
280 with EPZICOM (see CLINICAL PHARMACOLOGY for information about bioequivalence of  
281 EPZICOM). One EPZICOM Tablet given once daily is an alternative regimen to EPIVIR Tablets  
282 300 mg once daily plus ZIAGEN Tablets 2 x 300 mg once daily as a component of antiretroviral  
283 therapy.

284 The following study was conducted with the individual components of EPZICOM.

285 **Therapy-Naive Adults: CNA30021** was an international, multi-center, double-blind,  
286 controlled study in which 770 HIV-1-infected, therapy-naive adults were randomized and  
287 received either ZIAGEN 600 mg once daily or ZIAGEN 300 mg twice daily, both in  
288 combination with EPIVIR 300 mg once daily and efavirenz 600 mg once daily. The double-blind  
289 treatment duration was at least 48 weeks. Study participants had a mean age of 37 years, were:  
290 male (81%), Caucasian (54%), black (27%), and American Hispanic (15%). The median baseline  
291 CD4+ cell count was 262 cells/mm<sup>3</sup> (range: 21 to 918 cells/mm<sup>3</sup>) and the median baseline  
292 plasma HIV-1 RNA was 4.89 log<sub>10</sub> copies/mL (range: 2.60 to 6.99 log<sub>10</sub> copies/mL).

293 The outcomes of randomized treatment are provided in Table 3.

294

295 **Table 3. Outcomes of Randomized Treatment Through Week 48 (CNA30021)**

Outcome	ZIAGEN 600 mg q.d. plus EPIVIR plus Efavirenz (n = 384)	ZIAGEN 300 mg b.i.d. plus EPIVIR plus Efavirenz (n = 386)
Responder*	64% (71%)	65% (72%)
Virologic failure†	11% (5%)	11% (5%)
Discontinued due to adverse reactions	13%	11%
Discontinued due to other reasons‡	11%	13%

296 \* Patients achieved and maintained confirmed HIV-1 RNA <50 copies/mL (<400 copies/mL)  
 297 through Week 48 (Roche AMPLICOR Ultrasensitive HIV-1 MONITOR® standard test  
 298 version 1.0).

299 † Includes viral rebound, failure to achieve confirmed <50 copies/mL (<400 copies/mL) by  
 300 Week 48, and insufficient viral load response.

301 ‡ Includes consent withdrawn, lost to follow-up, protocol violations, clinical progression, and  
 302 other.

303        After 48 weeks of therapy, the median CD4+ cell count increases from baseline were  
 304 188 cells/mm<sup>3</sup> in the group receiving ZIAGEN 600 mg once daily and 200 cells/mm<sup>3</sup> in the  
 305 group receiving ZIAGEN 300 mg twice daily. Through Week 48, 6 subjects (2%) in the group  
 306 receiving ZIAGEN 600 mg once daily (4 CDC classification C events and 2 deaths) and  
 307 10 subjects (3%) in the group receiving ZIAGEN 300 mg twice daily (7 CDC classification C  
 308 events and 3 deaths) experienced clinical disease progression. None of the deaths were attributed  
 309 to study medications.

## 311 **CONTRAINDICATIONS**

312        EPZICOM Tablets are contraindicated in patients with previously demonstrated  
 313 hypersensitivity to abacavir or to any other component of the product (see WARNINGS).  
 314 NEVER restart EPZICOM or any other abacavir-containing product following a  
 315 hypersensitivity reaction to abacavir, regardless of HLA-B\*5701 status (see WARNINGS,  
 316 PRECAUTIONS, and ADVERSE REACTIONS).

317        EPZICOM Tablets are contraindicated in patients with hepatic impairment (see CLINICAL  
 318 PHARMACOLOGY).

## 319 **WARNINGS**

320        **Hypersensitivity Reaction:** Serious and sometimes fatal hypersensitivity reactions have  
 321 been associated with EPZICOM and other abacavir-containing products. Patients who  
 322 carry the HLA-B\*5701 allele are at high risk for experiencing a hypersensitivity reaction to  
 323 abacavir. Prior to initiating therapy with abacavir, screening for the HLA-B\*5701 allele is  
 324 recommended; this approach has been found to decrease the risk of a hypersensitivity

325 reaction. Screening is also recommended prior to reinitiation of abacavir in patients of  
326 unknown HLA-B\*5701 status who have previously tolerated abacavir. For  
327 HLA-B\*5701-positive patients, treatment with an abacavir-containing regimen is not  
328 recommended and should be considered only with close medical supervision and under  
329 exceptional circumstances when the potential benefit outweighs the risk.

330 HLA-B\*5701-negative patients may develop a hypersensitivity reaction to abacavir;  
331 however, this occurs significantly less frequently than in HLA-B\*5701-positive patients.  
332 Regardless of HLA-B\*5701 status, permanently discontinue EPZICOM if hypersensitivity  
333 cannot be ruled out, even when other diagnoses are possible.

334 Important information on signs and symptoms of hypersensitivity, as well as clinical  
335 management, is presented below.

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

339       **Group 1: Fever**

340       **Group 2: Rash**

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

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

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

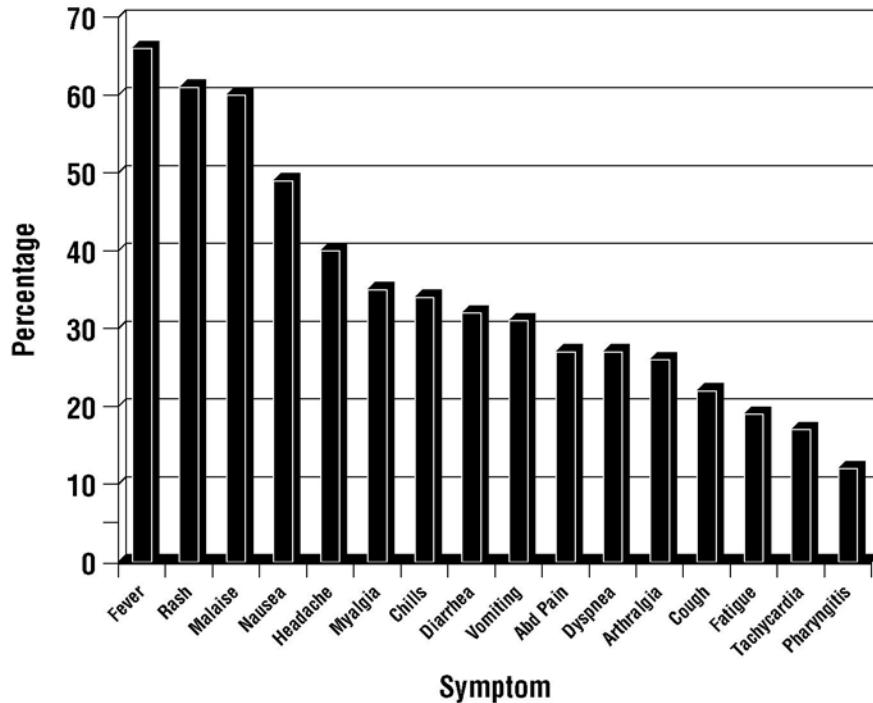
344

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

347       Hypersensitivity to abacavir was reported in approximately 8% of 2,670 patients (n = 206) in  
348 9 clinical trials (range: 2% to 9%) with enrollment from November 1999 to February 2002. Data  
349 on time to onset and symptoms of suspected hypersensitivity were collected on a detailed data  
350 collection module. The frequencies of symptoms are shown in Figure 1. Symptoms usually  
351 appeared within the first 6 weeks of treatment with abacavir, although the reaction may occur at  
352 any time during therapy. Median time to onset was 9 days; 89% appeared within the first  
353 6 weeks; 95% of patients reported symptoms from 2 or more of the 5 groups listed above.

354

355 **Figure 1: Hypersensitivity-Related Symptoms Reported with**  
356 **≥10% Frequency in Clinical Trials (n = 206 Patients)**



357  
358  
359 Other less common signs and symptoms of hypersensitivity include lethargy, myolysis,  
360 edema, abnormal chest x-ray findings (predominantly infiltrates, which can be localized), and  
361 paresthesia.

362 Anaphylaxis, liver failure, renal failure, hypotension, adult respiratory distress syndrome,  
363 respiratory failure, and death have occurred in association with hypersensitivity reactions. In one  
364 study, 4 patients (11%) receiving ZIAGEN 600 mg once daily experienced hypotension with a  
365 hypersensitivity reaction compared with 0 patients receiving ZIAGEN 300 mg twice daily.

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

371 Laboratory abnormalities associated with hypersensitivity to abacavir in some patients include  
372 elevated liver function tests, elevated creatine phosphokinase, elevated creatinine, and  
373 lymphopenia.

374 **Clinical Management of Hypersensitivity:** Discontinue EPZICOM as soon as a  
375 hypersensitivity reaction is suspected. To minimize the risk of a life-threatening  
376 hypersensitivity reaction, permanently discontinue EPZICOM if hypersensitivity cannot be  
377 ruled out, even when other diagnoses are possible (e.g., acute onset respiratory diseases

378 such as pneumonia, bronchitis, pharyngitis, or influenza; gastroenteritis; or reactions to  
379 other medications).

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

383 When therapy with EPZICOM has been discontinued for reasons other than symptoms of a  
384 hypersensitivity reaction, and if reinitiation of EPZICOM or any other abacavir-containing  
385 product is under consideration, carefully evaluate the reason for discontinuation of EPZICOM to  
386 ensure that the patient did not have symptoms of a hypersensitivity reaction. If the patient is of  
387 unknown HLA-B\*5701 status, screening for the allele is recommended prior to reinitiation of  
388 EPZICOM.

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

393 If symptoms consistent with hypersensitivity are not identified, reintroduction can be  
394 undertaken with continued monitoring for symptoms of a hypersensitivity reaction. Make  
395 patients aware that a hypersensitivity reaction can occur with reintroduction of EPZICOM or any  
396 other abacavir-containing product and that reintroduction of EPZICOM or introduction of any  
397 other abacavir-containing product needs to be undertaken only if medical care can be readily  
398 accessed by the patient or others.

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

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

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

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

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

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

425 **Lactic Acidosis/Severe Hepatomegaly With Steatosis:** Lactic acidosis and severe  
426 hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside  
427 analogues alone or in combination, including abacavir and lamivudine and other antiretrovirals.  
428 A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may  
429 be risk factors. Particular caution should be exercised when administering EPZICOM to any  
430 patient with known risk factors for liver disease; however, cases have also been reported in  
431 patients with no known risk factors. Treatment with EPZICOM should be suspended in any  
432 patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced  
433 hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked  
434 transaminase elevations).

435 **Posttreatment Exacerbations of Hepatitis:** In clinical trials in non-HIV-1-infected  
436 patients treated with lamivudine for chronic HBV, clinical and laboratory evidence of  
437 exacerbations of hepatitis have occurred after discontinuation of lamivudine. These  
438 exacerbations have been detected primarily by serum ALT elevations in addition to  
439 re-emergence of HBV DNA. Although most events appear to have been self-limited, fatalities  
440 have been reported in some cases. Similar events have been reported from post-marketing  
441 experience after changes from lamivudine-containing HIV-1 treatment regimens to  
442 non-lamivudine-containing regimens in patients infected with both HIV-1 and HBV. The causal  
443 relationship to discontinuation of lamivudine treatment is unknown. Patients should be closely  
444 monitored with both clinical and laboratory follow-up for at least several months after stopping  
445 treatment. There is insufficient evidence to determine whether re-initiation of lamivudine alters  
446 the course of posttreatment exacerbations of hepatitis.

447 **Use With Interferon- and Ribavirin-Based Regimens:** In vitro studies have shown  
448 ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine,  
449 a component of EPZICOM. Although no evidence of a pharmacokinetic or pharmacodynamic  
450 interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was  
451 coadministered with lamivudine in HIV-1/HCV co-infected patients (see CLINICAL  
452 PHARMACOLOGY: Drug Interactions), **hepatic decompensation (some fatal) has occurred**  
453 **in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1**  
454 **and interferon alfa with or without ribavirin.** Patients receiving interferon alfa with or without  
455 ribavirin and EPZICOM should be closely monitored for treatment-associated toxicities,  
456 especially hepatic decompensation. Discontinuation of EPZICOM should be considered as  
457 medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both  
458 should also be considered if worsening clinical toxicities are observed, including hepatic  
459 decompensation (e.g., Childs Pugh >6) (see the complete prescribing information for interferon  
460 and ribavirin).

461 **Other:** EPZICOM contains fixed doses of 2 nucleoside analogues, abacavir and lamivudine, and  
462 should not be administered concomitantly with other abacavir-containing and/or  
463 lamivudine-containing products (ZIAGEN, EPIVIR, COMBIVIR<sup>®</sup>, or TRIZIVIR).

464 The complete prescribing information for all agents being considered for use with EPZICOM  
465 should be consulted before combination therapy with EPZICOM is initiated.

## 466 PRECAUTIONS

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

472 **Patients With HIV-1 and Hepatitis B Virus Co-infection: Lamivudine:** Safety and  
473 efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients  
474 dually infected with HIV-1 and HBV. In non-HIV-1-infected patients treated with lamivudine  
475 for chronic hepatitis B, emergence of lamivudine-resistant HBV has been detected and has been  
476 associated with diminished treatment response (see EPIVIR-HBV package insert for additional  
477 information). Emergence of hepatitis B virus variants associated with resistance to lamivudine  
478 has also been reported in HIV-1-infected patients who have received lamivudine-containing  
479 antiretroviral regimens in the presence of concurrent infection with hepatitis B virus.

480 **Patients With Impaired Renal Function: EPZICOM:** Since EPZICOM is a fixed-dose  
481 tablet and the dosage of the individual components cannot be altered, patients with creatinine  
482 clearance <50 mL/min should not receive EPZICOM.

483 **Patients With Impaired Hepatic Function: EPZICOM:** EPZICOM is contraindicated in  
484 patients with hepatic impairment since it is a fixed-dose tablet and the dosage of the individual  
485 components cannot be altered.

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

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

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

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

506 **Information for Patients:**

507 **Abacavir: Hypersensitivity Reaction:** Inform patients:

- 508 • that a Medication Guide and Warning Card summarizing the symptoms of the abacavir  
509 hypersensitivity reaction and other product information will be dispensed by the  
510 pharmacist with each new prescription and refill of EPZICOM, and encourage the  
511 patient to read the Medication Guide and Warning Card every time to obtain any new  
512 information that may be present about EPZICOM. (The complete text of the Medication  
513 Guide is reprinted at the end of this document.)
- 514 • to carry the Warning Card with them.
- 515 • how to identify a hypersensitivity reaction (see WARNINGS and MEDICATION GUIDE).
- 516 • that if they develop symptoms consistent with a hypersensitivity reaction they should call their  
517 doctor right away to determine if they should stop taking EPZICOM.
- 518 • that a hypersensitivity reaction can worsen and lead to hospitalization or death if EPZICOM is  
519 not immediately discontinued.
- 520 • to not restart EPZICOM or any other abacavir-containing product following a  
521 hypersensitivity reaction because more severe symptoms can occur within hours and may  
522 include life-threatening hypotension and death.
- 523 • that a hypersensitivity reaction is usually reversible if it is detected promptly and EPZICOM is  
524 stopped right away.

- 525 • that if they have interrupted EPZICOM for reasons other than symptoms of hypersensitivity  
526 (for example, those who have an interruption in drug supply), a serious or fatal  
527 hypersensitivity reaction may occur with reintroduction of abacavir.  
528 • that in one study, more severe hypersensitivity reactions were seen when ZIAGEN was dosed  
529 600 mg once daily.  
530 • **to not restart EPZICOM or any other abacavir-containing product without medical**  
531 **consultation and that restarting abacavir needs to be undertaken only if medical care can**  
532 **be readily accessed by the patient or others.**

533 **Lamivudine:** Patients co-infected with HIV-1 and HBV should be informed that  
534 deterioration of liver disease has occurred in some cases when treatment with lamivudine was  
535 discontinued. Patients should be advised to discuss any changes in regimen with their physician.

536 **EPZICOM:** Inform patients that some HIV-1 medicines, including EPZICOM, can cause a  
537 rare, but serious condition called lactic acidosis with liver enlargement (hepatomegaly).

538 EPZICOM is not a cure for HIV-1 infection and patients may continue to experience illnesses  
539 associated with HIV-1 infection, including opportunistic infections. Patients should remain under  
540 the care of a physician when using EPZICOM. Advise patients that the use of EPZICOM has not  
541 been shown to reduce the risk of transmission of HIV-1 to others through sexual contact or blood  
542 contamination.

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

546 EPZICOM Tablets are for oral ingestion only.

547 Patients should be advised of the importance of taking EPZICOM exactly as it is prescribed.

548 **Drug Interactions:** **EPZICOM:** No clinically significant changes to pharmacokinetic  
549 parameters were observed for abacavir or lamivudine when administered together.

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

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

559 **Lamivudine:** Trimethoprim (TMP) 160 mg/sulfamethoxazole (SMX) 800 mg once daily has  
560 been shown to increase lamivudine exposure (AUC). No change in dose of either drug is  
561 recommended. The effect of higher doses of TMP/SMX on lamivudine pharmacokinetics has not  
562 been investigated (see CLINICAL PHARMACOLOGY).

563 Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another.  
564 Therefore, use of EPZICOM in combination with zalcitabine is not recommended.

565 See CLINICAL PHARMACOLOGY for additional drug interactions.

566 **Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity:**

567 **Abacavir:** Abacavir was administered orally at 3 dosage levels to separate groups of mice  
568 and rats in 2-year carcinogenicity studies. Results showed an increase in the incidence of  
569 malignant and non-malignant tumors. Malignant tumors occurred in the preputial gland of males  
570 and the clitoral gland of females of both species, and in the liver of female rats. In addition,  
571 non-malignant tumors also occurred in the liver and thyroid gland of female rats. These  
572 observations were made at systemic exposures in the range of 6 to 32 times the human exposure  
573 at the recommended dose.

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

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

579 **Mutagenicity: Abacavir:** Abacavir induced chromosomal aberrations both in the presence  
580 and absence of metabolic activation in an in vitro cytogenetic study in human lymphocytes.  
581 Abacavir was mutagenic in the absence of metabolic activation, although it was not mutagenic in  
582 the presence of metabolic activation in an L5178Y mouse lymphoma assay. Abacavir was  
583 clastogenic in males and not clastogenic in females in an in vivo mouse bone marrow  
584 micronucleus assay. Abacavir was not mutagenic in bacterial mutagenicity assays in the presence  
585 and absence of metabolic activation.

586 **Lamivudine:** Lamivudine was mutagenic in an L5178Y mouse lymphoma assay and  
587 clastogenic in a cytogenetic assay using cultured human lymphocytes. Lamivudine was not  
588 mutagenic in a microbial mutagenicity assay, in an in vitro cell transformation assay, in a rat  
589 micronucleus test, in a rat bone marrow cytogenetic assay, and in an assay for unscheduled DNA  
590 synthesis in rat liver.

591 **Impairment of Fertility:** Abacavir or lamivudine induced no adverse effects on the mating  
592 performance or fertility of male and female rats at doses producing systemic exposure levels  
593 approximately 8 or 130 times, respectively, higher than those in humans at the recommended  
594 dose based on body surface area comparisons.

595 **Pregnancy:** Pregnancy Category C. There are no adequate and well-controlled studies of  
596 EPZICOM in pregnant women. Reproduction studies with abacavir and lamivudine have been  
597 performed in animals (see Abacavir and Lamivudine sections below). EPZICOM should be used  
598 during pregnancy only if the potential benefits outweigh the risks.

599 **Abacavir:** Studies in pregnant rats showed that abacavir is transferred to the fetus through  
600 the placenta. Fetal malformations (increased incidences of fetal anasarca and skeletal  
601 malformations) and developmental toxicity (depressed fetal body weight and reduced  
602 crown-rump length) were observed in rats at a dose which produced 35 times the human  
603 exposure, based on AUC. Embryonic and fetal toxicities (increased resorptions, decreased fetal  
604 body weights) and toxicities to the offspring (increased incidence of stillbirth and lower body

605 weights) occurred at half of the above-mentioned dose in separate fertility studies conducted in  
606 rats. In the rabbit, no developmental toxicity and no increases in fetal malformations occurred at  
607 doses that produced 8.5 times the human exposure at the recommended dose based on AUC.

608 **Lamivudine:** Studies in pregnant rats showed that lamivudine is transferred to the fetus  
609 through the placenta. Reproduction studies with orally administered lamivudine have been  
610 performed in rats and rabbits at doses producing plasma levels up to approximately 35 times that  
611 for the recommended adult HIV dose. No evidence of teratogenicity due to lamivudine was  
612 observed. Evidence of early embryolethality was seen in the rabbit at exposure levels similar to  
613 those observed in humans, but there was no indication of this effect in the rat at exposure levels  
614 up to 35 times those in humans.

615 **Antiretroviral Pregnancy Registry:** To monitor maternal-fetal outcomes of pregnant  
616 women exposed to EPZICOM or other antiretroviral agents, an Antiretroviral Pregnancy  
617 Registry has been established. Physicians are encouraged to register patients by calling 1-800-  
618 258-4263.

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

622 **Abacavir:** Abacavir is secreted into the milk of lactating rats.

623 **Lamivudine:** Lamivudine is excreted in human breast milk and into the milk of lactating  
624 rats.

625 Because of both the potential for HIV-1 transmission and the potential for serious adverse  
626 reactions in nursing infants, **mothers should be instructed not to breastfeed if they are**  
627 **receiving EPZICOM.**

628 **Pediatric Use:** Safety and effectiveness of EPZICOM in pediatric patients have not been  
629 established.

630 **Geriatric Use:** Clinical studies of abacavir and lamivudine did not include sufficient numbers  
631 of patients aged 65 and over to determine whether they respond differently from younger  
632 patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater  
633 frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other  
634 drug therapy. EPZICOM is not recommended for patients with impaired renal function or  
635 impaired hepatic function (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

## 636 **ADVERSE REACTIONS**

637 **Abacavir: Hypersensitivity Reaction:** Serious and sometimes fatal hypersensitivity  
638 reactions have been associated with abacavir sulfate, a component of EPZICOM.

639 **In one study, once-daily dosing of ZIAGEN was associated with more severe  
640 hypersensitivity reactions (see WARNINGS and PRECAUTIONS: Information for  
641 Patients).**

642 **Therapy-Naïve Adults:** Treatment-emergent clinical adverse reactions (rated by the  
643 investigator as moderate or severe) with a ≥5% frequency during therapy with ZIAGEN 600 mg

644 once daily or ZIAGEN 300 mg twice daily, both in combination with lamivudine 300 mg once  
645 daily and efavirenz 600 mg once daily are listed in Table 4.

646

647 **Table 4. Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate  
648 Intensity (Grades 2-4, ≥5% Frequency) in Therapy-Naive Adults (CNA30021) Through  
649 48 Weeks of Treatment**

Adverse Event	ZIAGEN 600 mg q.d. plus EPIVIR plus Efavirenz (n = 384)	ZIAGEN 300 mg b.i.d. plus EPIVIR plus Efavirenz (n = 386)
<b>Drug hypersensitivity*†</b>	9%	7%
Insomnia	7%	9%
Depression/Depressed mood	7%	7%
Headache/Migraine	7%	6%
Fatigue/Malaise	6%	8%
Dizziness/Vertigo	6%	6%
Nausea	5%	6%
Diarrhea*	5%	6%
Rash	5%	5%
Pyrexia	5%	3%
Abdominal pain/gastritis	4%	5%
Abnormal dreams	4%	5%
Anxiety	3%	5%

650 \* Patients receiving ZIAGEN 600 mg once daily, experienced a significantly higher incidence  
651 of severe drug hypersensitivity reactions and severe diarrhea compared with patients who  
652 received ZIAGEN 300 mg twice daily. Five percent (5%) of patients receiving ZIAGEN  
653 600 mg once daily had severe drug hypersensitivity reactions compared with 2% of patients  
654 receiving ZIAGEN 300 mg twice daily. Two percent (2%) of patients receiving ZIAGEN  
655 600 mg once daily had severe diarrhea while none of the patients receiving ZIAGEN 300 mg  
656 twice daily had this event.

657 † **Study CNA30024** was a multi-center, double-blind, controlled study in which  
658 649 HIV-1-infected, therapy-naive adults were randomized and received either ZIAGEN  
659 (300 mg twice daily), EPIVIR (150 mg twice daily), and efavirenz (600 mg once daily) or  
660 zidovudine (300 mg twice daily), EPIVIR (150 mg twice daily), and efavirenz (600 mg once  
661 daily). CNA30024 used double-blind ascertainment of suspected hypersensitivity reactions.  
662 During the blinded portion of the study, **suspected hypersensitivity to abacavir was  
663 reported by investigators in 9% of 324 patients in the abacavir group and 3% of  
664 325 patients in the zidovudine group.**

665

666 **Laboratory Abnormalities:** Laboratory abnormalities observed in clinical studies of  
667 ZIAGEN were anemia, neutropenia, liver function test abnormalities, and elevations of CPK,  
668 blood glucose, and triglycerides. Additional laboratory abnormalities observed in clinical studies  
669 of EPIVIR were thrombocytopenia and elevated levels of bilirubin, amylase, and lipase.

670 The frequencies of treatment-emergent laboratory abnormalities were comparable between  
671 treatment groups in Study CNA30021.

672 **Other Adverse Events:** In addition to adverse reactions listed above, other adverse events  
673 observed in the expanded access program for abacavir were pancreatitis and increased GGT.

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

679 **Abacavir:**

680 **Cardiovascular:** Myocardial infarction.

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

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

688 **Abacavir and Lamivudine:**

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

691 **Digestive:** Stomatitis.

692 **Endocrine and Metabolic:** Hyperglycemia.

693 **General:** Weakness.

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

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

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

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

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

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

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

703 **OVERDOSAGE**

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

706 **Lamivudine:** One case of an adult ingesting 6 grams of lamivudine was reported; there were no  
707 clinical signs or symptoms noted and hematologic tests remained normal. It is not known  
708 whether lamivudine can be removed by peritoneal dialysis or hemodialysis.

709 **DOSAGE AND ADMINISTRATION**

710 **A Medication Guide and Warning Card that provide information about recognition of**  
711 **hypersensitivity reactions should be dispensed with each new prescription and refill.** To  
712 facilitate reporting of hypersensitivity reactions and collection of information on each case, an  
713 Abacavir Hypersensitivity Registry has been established. **Physicians should register patients**  
714 **by calling 1-800-270-0425.**

715 The recommended oral dose of EPZICOM for adults is one tablet daily, in combination with  
716 other antiretroviral agents (see INDICATIONS AND USAGE: Description of Clinical Studies,  
717 PRECAUTIONS, MICROBIOLOGY, and CLINICAL PHARMACOLOGY).

718 EPZICOM can be taken with or without food.

719 **Dose Adjustment:** Because it is a fixed-dose tablet, EPZICOM should not be prescribed for  
720 patients requiring dosage adjustment such as those with creatinine clearance <50 mL/min, those  
721 with hepatic impairment, or those experiencing dose-limiting adverse events. Use of EPIVIR  
722 Oral Solution and ZIAGEN Oral Solution may be considered.

723 **HOW SUPPLIED**

724 EPZICOM is available as tablets. Each tablet contains 600 mg of abacavir as abacavir sulfate  
725 and 300 mg of lamivudine. The tablets are orange, film-coated, modified capsule-shaped, and  
726 debossed with GS FC2 on one side with no markings on the reverse side. They are packaged as  
727 follows:

728 Bottles of 30 Tablets (NDC 0173-0742-00).

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

731 **ANIMAL TOXICOLOGY**

732 Myocardial degeneration was found in mice and rats following administration of abacavir for  
733 2 years. The systemic exposures were equivalent to 7 to 24 times the expected systemic exposure  
734 in humans. The clinical relevance of this finding has not been determined.

735 **REFERENCE**

- 736 1. Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study Group. *Lancet*.  
737 2008;371 (9622):1417-1426.

738

739 Revised March 2009

740

## MEDICATION GUIDE

## **EPZICOM® (ep' zih com) Tablets**

**Generic name:** abacavir (uh-BACK-ah-veer) sulfate and lamivudine (la-MIV-yoo-deen)

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

752 What is the most important information I should know about EPZICOM?

- **Serious Allergic Reaction to Abacavir.** EPZICOM contains abacavir (also contained in ZIAGEN® and TRIZIVIR®). Patients taking EPZICOM 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 EPZICOM, call your doctor right away to determine if you should stop taking this medicine.**

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

761  
762 A list of these symptoms is on the Warning Card your pharmacist gives you. Carry this  
763 Warning Card with you.

**If you stop EPZICOM because of an allergic reaction, NEVER take EPZICOM (abacavir sulfate and lamivudine) or any other abacavir-containing medicine (ZIAGEN and TRIZIVIR) again.** If you take EPZICOM 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 EPZICOM for any other reason, even for a few days, and you are not allergic to EPZICOM, talk with your doctor before taking it again. Taking**

773      **EPZICOM again can cause a serious allergic or life-threatening reaction, even if you**  
774      **never had an allergic reaction to it before.** If your doctor tells you that you can take  
775      EPZICOM again, **start taking it when you are around medical help or people who can**  
776      **call a doctor if you need one.**

- 777
- 778    • **Lactic Acidosis. Some human immunodeficiency virus (HIV) medicines, including**  
779      **EPZICOM, can cause a rare but serious condition called lactic acidosis with liver**  
780      **enlargement (hepatomegaly).** Nausea and tiredness that don't get better may be symptoms of  
781      lactic acidosis. In some cases this condition can cause death. Women, overweight people, and  
782      people who have taken HIV medicines like EPZICOM for a long time have a higher chance of  
783      getting lactic acidosis and liver enlargement. Lactic acidosis is a medical emergency and must  
784      be treated in the hospital.

785

  - 786    • **Worsening of hepatitis B virus (HBV) infection.** Patients with HBV infection, who take  
787      EPZICOM and then stop it, may get "flare-ups" of their hepatitis. "Flare-up" is when the  
788      disease suddenly returns in a worse way than before. If you have HBV infection, your doctor  
789      should closely monitor your liver function for several months after stopping EPZICOM. You  
790      may need to take anti-HBV medicines.

791

  - 792    • **Use with interferon- and ribavirin-based regimens.** Worsening of liver disease (sometimes  
793      resulting in death) has occurred in patients infected with both HIV and hepatitis C virus who  
794      are taking anti-HIV medicines and are also being treated for hepatitis C with interferon with or  
795      without ribavirin. If you are taking EPZICOM as well as interferon with or without ribavirin  
796      and you experience side effects, be sure to tell your doctor.

797

798      EPZICOM can have other serious side effects. Be sure to read the section below entitled "What  
799      are the possible side effects of EPZICOM?"

800

801      **What is EPZICOM?**

802      EPZICOM is a prescription medicine used to treat HIV infection. EPZICOM includes  
803      2 medicines: abacavir (ZIAGEN) and lamivudine or 3TC (EPIVIR®). See the end of this  
804      Medication Guide for a complete list of ingredients in EPZICOM. Both of these medicines are  
805      called nucleoside analogue reverse transcriptase inhibitors (NRTIs). When used together, they  
806      help lower the amount of HIV in your blood. This helps to keep your immune system as healthy  
807      as possible so that it can help fight infection.

808

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

- 812 • **EPZICOM does not cure HIV infection or AIDS.** We do not know if EPZICOM will help  
813 you live longer or have fewer of the medical problems that people get with HIV or AIDS. It is  
814 very important that you see your doctor regularly while you are taking EPZICOM.  
815 • **EPZICOM does not lower the risk of passing HIV to other people through sexual**  
816 **contact, sharing needles, or being exposed to your blood.** For your health and the health of  
817 others, it is important to always practice safe sex by using a latex or polyurethane condom or  
818 other barrier method to lower the chance of sexual contact with semen, vaginal secretions, or  
819 blood. Never use or share dirty needles.

820

821 **Who should not take EPZICOM?**

822 **Do not take EPZICOM if you:**

- 823 • **have ever had a serious allergic reaction (a hypersensitivity reaction) to EPZICOM or**  
824 **any other medicine that has abacavir as one of its ingredients (TRIZIVIR and ZIAGEN).**  
825 See the end of this Medication Guide for a complete list of ingredients in EPZICOM.  
826 • **have a liver that does not function properly.**  
827 • **are less than 18 years of age.**

828

829 **Before starting EPZICOM tell your doctor about all of your medical conditions, including**  
830 **if you:**

- 831 • **have been tested and know whether or not you have a particular gene variation called**  
832 **HLA-B\*5701.**  
833 • **are pregnant or planning to become pregnant.** We do not know if EPZICOM will harm  
834 your unborn child. You and your doctor will need to decide if EPZICOM is right for you. If  
835 you use EPZICOM while you are pregnant, talk to your doctor about how you can be on the  
836 Antiviral Pregnancy Registry for EPZICOM.  
837 • **are breastfeeding.** Some of the ingredients in EPZICOM can be passed to your baby in your  
838 breast milk. It is not known if they could harm your baby. Also, mothers with HIV should not  
839 breastfeed because HIV can be passed to the baby in the breast milk.  
840 • **have liver problems including hepatitis B virus infection.**  
841 • **have kidney problems.**  
842 • **have heart problems, smoke, or suffer from diseases that increase your risk of heart**  
843 **disease such as high blood pressure, high cholesterol, or diabetes.**

844

845 **Tell your doctor about all the medicines you take, including prescription and**  
846 **nonprescription medicines, vitamins, and herbal supplements. Especially tell your doctor if**  
847 **you take any of the following medicines\*:**

- 848 • **methadone**  
849 • **HIVID® (zalcitabine, ddC)**

- 850 • **EPIVIR or EPIVIR-HBV® (lamivudine, 3TC), ZIAGEN (abacavir sulfate), COMBIVIR®**  
851     (lamivudine and zidovudine), or TRIZIVIR (abacavir sulfate, lamivudine, and  
852     zidovudine).

853

854 **How should I take EPZICOM?**

- 855 • Take EPZICOM by mouth exactly as your doctor prescribes it. The usual dose is 1 tablet  
856     once a day. Do not skip doses.
- 857 • You can take EPZICOM with or without food.
- 858 • If you miss a dose of EPZICOM, take the missed dose right away. Then, take the next  
859     dose at the usual time.
- 860 • Do not let your EPZICOM run out.
- 861 • Starting EPZICOM again can cause a serious allergic or life-threatening reaction, even if  
862     you never had an allergic reaction to it before. If you run out of EPZICOM even for a few  
863     days, you must ask your doctor if you can start EPZICOM again. If your doctor tells you that  
864     you can take EPZICOM again, start taking it when you are around medical help or people who  
865     can call a doctor if you need one.
- 866 • If you stop your anti-HIV drugs, even for a short time, the amount of virus in your blood  
867     may increase and the virus may become harder to treat.
- 868 • If you take too much EPZICOM, call your doctor or poison control center right away.

869

870 **What should I avoid while taking EPZICOM?**

- 871 • Do not take EPIVIR (lamivudine, 3TC), COMBIVIR (lamivudine and zidovudine),  
872     ZIAGEN (abacavir sulfate), or TRIZIVIR (abacavir sulfate, lamivudine, and zidovudine)  
873     while taking EPZICOM. Some of these medicines are already in EPZICOM.
- 874 • Do not take zalcitabine (Hivid, ddC) while taking EPZICOM.

875

876 **Avoid doing things that can spread HIV infection**, as EPZICOM does not stop you from  
877 passing the HIV infection to others.

- 878 • Do not share needles or other injection equipment.
- 879 • Do not share personal items that can have blood or body fluids on them, like  
880     toothbrushes and razor blades.
- 881 • Do not have any kind of sex without protection. Always practice safe sex by using a latex or  
882     polyurethane condom or other barrier method to lower the chance of sexual contact with  
883     semen, vaginal secretions, or blood.
- 884 • Do not breastfeed. EPZICOM can be passed to babies in breast milk and could harm the  
885     baby. Also, mothers with HIV should not breastfeed because HIV can be passed to the baby in  
886     the breast milk.

887

888 **What are the possible side effects of EPZICOM?**

889 EPZICOM can cause the following serious side effects:

- 890 • **Serious allergic reaction that can cause death.** (See "What is the most important information  
891 I should know about EPZICOM?" at the beginning of this Medication Guide.)  
892 • **Lactic acidosis with liver enlargement (hepatomegaly) that can cause death.** (See "What is  
893 the most important information I should know about EPZICOM?" at the beginning of this  
894 Medication Guide.)  
895 • **Worsening of HBV infection.** (See "What is the most important information I should know  
896 about EPZICOM?" at the beginning of this Medication Guide.)  
897 • **Changes in immune system.** When you start taking HIV medicines, your immune system  
898 may get stronger and could begin to fight infections that have been hidden in your body, such  
899 as pneumonia, herpes virus, or tuberculosis. If you have new symptoms after starting your HIV  
900 medicines, be sure to tell your doctor.  
901 • **Changes in body fat.** These changes have happened in patients taking antiretroviral medicines  
902 like EPZICOM. The changes may include an increased amount of fat in the upper back and  
903 neck ("buffalo hump"), breast, and around the back, chest, and stomach area. Loss of fat from  
904 the legs, arms, and face may also happen. The cause and long-term health effects of these  
905 conditions are not known.

906  
907 Some HIV medicines including EPZICOM may increase your risk of heart attack. If you have  
908 heart problems, smoke, or suffer from diseases that increase your risk of heart disease such as  
909 high blood pressure, high cholesterol, or diabetes, tell your doctor.

910  
911 The most common side effects with EPZICOM are trouble sleeping, depression, headache,  
912 tiredness, dizziness, nausea, diarrhea, rash, fever, stomach pain, abnormal dreams, and anxiety.  
913 Most of these side effects did not cause people to stop taking EPZICOM.

914  
915 This list of side effects is not complete. Call your doctor for medical advice about side effects.  
916 You may report side effects to FDA at 1-800-FDA-1088.

917  
**How should I store EPZICOM?**

- 918  
919 • Store EPZICOM at room temperature between 59° to 86°F (15° to 30°C).  
920 • Keep EPZICOM and all medicines out of the reach of children.

921  
**General information for safe and effective use of EPZICOM**

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

925  
926 This Medication Guide summarizes the most important information about EPZICOM. If you  
927 would like more information, talk with your doctor. You can ask your doctor or pharmacist for  
928 the information that is written for healthcare professionals or call 1-888-825-5249.

930

931 **What are the ingredients in EPZICOM?**

932 **Active ingredients:** abacavir sulfate and lamivudine

933 **Inactive ingredients:** Each film-coated EPZICOM Tablet contains the inactive ingredients  
934 magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The tablets are  
935 coated with a film (OPADRY® orange YS-1-13065-A) that is made of FD&C Yellow No. 6,  
936 hypromellose, polyethylene glycol 400, polysorbate 80, and titanium dioxide.

937

938

939

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

941

942 COMBIVIR, EPIVIR, EPZICOM, RETROVIR, TRIZIVIR, and ZIAGEN are registered  
943 trademarks of GlaxoSmithKline.

944

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947 GlaxoSmithKline or its products.

948

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954 Lamivudine is manufactured under agreement from

955 **Shire Pharmaceuticals Group plc**

956

Basingstoke, UK

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960 March 2009

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