

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EPZICOM safely and effectively. See full prescribing information for EPZICOM.

EPZICOM (abacavir sulfate and lamivudine) Tablets, for oral use
Initial U.S. Approval: 2004

WARNING: RISK OF HYPERSENSITIVITY REACTIONS, LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY, AND EXACERBATIONS OF HEPATITIS

See full prescribing information for complete boxed warning.

- Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir-containing products (5.1)
- Hypersensitivity to abacavir is a multi-organ clinical syndrome. (5.1)
- Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. (5.1)
- Discontinue EPZICOM as soon as a hypersensitivity reaction is suspected. Regardless of HLA-B*5701 status, permanently discontinue EPZICOM if hypersensitivity cannot be ruled out, even when other diagnoses are possible. (5.1)
- Following a hypersensitivity reaction to abacavir, NEVER restart EPZICOM or any other abacavir-containing product. (5.1)
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues. (5.2)
- 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, a component of EPZICOM. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.3)

RECENT MAJOR CHANGES

Warnings and Precautions, Immune Reconstitution Syndrome (5.5) ----- 11/2011

INDICATIONS AND USAGE

EPZICOM, a combination of abacavir and lamivudine, both nucleoside analogue HIV-1 reverse transcriptase inhibitors, is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. (1)

DOSAGE AND ADMINISTRATION

- A medication guide and warning card should be dispensed with each new prescription and refill. (2)
- Adults: One tablet daily. (2.1)

- Do not prescribe for patients requiring a dosage adjustment or patients with hepatic impairment. (2.2)

DOSAGE FORMS AND STRENGTHS

Tablets contain 600 mg of abacavir and 300 mg of lamivudine. (3)

CONTRAINDICATIONS

- Previously demonstrated hypersensitivity to abacavir or any other component of the product. (4, 5.1)
- Hepatic impairment. (4)

WARNINGS AND PRECAUTIONS

- See boxed warning for information about the following: hypersensitivity reactions, lactic acidosis and severe hepatomegaly, and severe acute exacerbations of hepatitis B. (5.1, 5.2, 5.3)
- Hepatic decompensation, some fatal, has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy and interferon alfa with or without ribavirin. Discontinue EPZICOM as medically appropriate and consider dose reduction or discontinuation of interferon alfa, ribavirin, or both. (5.4)
- Immune reconstitution syndrome (5.5) and redistribution/accumulation of body fat have been reported in patients treated with combination antiretroviral therapy. (5.6)
- EPZICOM should not be administered with other lamivudine- or zidovudine-containing products or emtricitabine-containing products. (5.8)

ADVERSE REACTIONS

The most commonly reported adverse reactions of at least moderate intensity (incidence >5%) in an adult HIV-1 clinical study were drug hypersensitivity, insomnia, depression/depressed mood, headache/migraine, fatigue/malaise, dizziness/vertigo, nausea, and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact ViiV Healthcare at 1-877-844-8872 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Ethanol: Decreases elimination of abacavir. (7.2)
- Methadone: An increased methadone dose may be required in a small number of patients. (7.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 03/2012

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1 **FULL PRESCRIBING INFORMATION**

2 **WARNING: RISK OF HYPERSENSITIVITY REACTIONS, LACTIC ACIDOSIS AND**
3 **SEVERE HEPATOMEGALY, AND EXACERBATIONS OF HEPATITIS B**

4 **Hypersensitivity Reactions:** Serious and sometimes fatal hypersensitivity reactions have
5 been associated with abacavir sulfate, a component of EPZICOM[®] (abacavir sulfate and
6 lamivudine) Tablets.

7 Hypersensitivity to abacavir is a multi-organ clinical syndrome usually
8 characterized by a sign or symptom in 2 or more of the following groups: (1) fever, (2)
9 rash, (3) gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain), (4)
10 constitutional (including generalized malaise, fatigue, or achiness), and (5) respiratory
11 (including dyspnea, cough, or pharyngitis). Discontinue EPZICOM as soon as a
12 hypersensitivity reaction is suspected.

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

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

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

26 Reintroduction of EPZICOM or any other abacavir-containing product, even in
27 patients who have no identified history or unrecognized symptoms of hypersensitivity to
28 abacavir therapy, can result in serious or fatal hypersensitivity reactions. Such reactions
29 can occur within hours [*see Warnings and Precautions (5.1)*].

30 **Lactic Acidosis and Severe Hepatomegaly:** Lactic acidosis and severe hepatomegaly
31 with steatosis, including fatal cases, have been reported with the use of nucleoside
32 analogues alone or in combination, including abacavir, lamivudine, and other
33 antiretrovirals [*see Warnings and Precautions (5.2)*].

34 **Exacerbations of Hepatitis B:** Severe acute exacerbations of hepatitis B have been
35 reported in patients who are co-infected with hepatitis B virus (HBV) and human
36 immunodeficiency virus (HIV-1) and have discontinued lamivudine, which is one
37 component of EPZICOM. Hepatic function should be monitored closely with both clinical
38 and laboratory follow-up for at least several months in patients who discontinue

39 **EPZICOM and are co-infected with HIV-1 and HBV. If appropriate, initiation of**
40 **anti-hepatitis B therapy may be warranted [see Warnings and Precautions (5.3)].**

41 **1 INDICATIONS AND USAGE**

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

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

- 46 • EPZICOM is one of multiple products containing abacavir. Before starting EPZICOM,
47 review medical history for prior exposure to any abacavir-containing product in order to
48 avoid reintroduction in a patient with a history of hypersensitivity to abacavir [see *Warnings*
49 *and Precautions (5.1), Adverse Reactions (6)*].
- 50 • As part of a triple-drug regimen, EPZICOM Tablets are recommended for use with
51 antiretroviral agents from different pharmacological classes and not with other
52 nucleoside/nucleotide reverse transcriptase inhibitors.

53 **2 DOSAGE AND ADMINISTRATION**

- 54 • A Medication Guide and Warning Card that provide information about recognition of
55 hypersensitivity reactions should be dispensed with each new prescription and refill.
- 56 • To facilitate reporting of hypersensitivity reactions and collection of information on each
57 case, an Abacavir Hypersensitivity Registry has been established. Physicians should register
58 patients by calling 1-800-270-0425.
- 59 • EPZICOM can be taken with or without food.

60 **2.1 Adult Patients**

61 The recommended oral dose of EPZICOM for adults is one tablet daily, in combination
62 with other antiretroviral agents.

63 **2.2 Dosage Adjustment**

64 Because it is a fixed-dose combination, EPZICOM should not be prescribed for:

- 65 • patients requiring dosage adjustment such as those with creatinine clearance <50 mL/min,
- 66 • patients with hepatic impairment.

67 Use of EPIVIR[®] (lamivudine) Oral Solution or Tablets and ZIAGEN[®] (abacavir sulfate)
68 Oral Solution may be considered.

69 **3 DOSAGE FORMS AND STRENGTHS**

70 EPZICOM Tablets contain 600 mg of abacavir as abacavir sulfate and 300 mg of
71 lamivudine. The tablets are modified capsule-shaped, orange, film-coated, and debossed with
72 “GS FC2” on one side with no markings on the reverse side.

73 **4 CONTRAINDICATIONS**

74 EPZICOM Tablets are contraindicated in patients with:

- 75 • previously demonstrated hypersensitivity to abacavir or to any other component of the
76 product. NEVER restart EPZICOM or any other abacavir-containing product following a
77 hypersensitivity reaction to abacavir, regardless of HLA-B*5701 status [see Warnings and
78 Precautions (5.1), Adverse Reactions (6)].
79 • hepatic impairment [see Use in Specific Populations (8.7)].

80 **5 WARNINGS AND PRECAUTIONS**

81 **5.1 Hypersensitivity Reaction**

82 Serious and sometimes fatal hypersensitivity reactions have been associated with
83 EPZICOM and other abacavir-containing products. Patients who carry the HLA-B*5701 allele
84 are at high risk for experiencing a hypersensitivity reaction to abacavir. Prior to initiating therapy
85 with abacavir, screening for the HLA-B*5701 allele is recommended; this approach has been
86 found to decrease the risk of a hypersensitivity reaction. Screening is also recommended prior to
87 reinitiation of abacavir in patients of unknown HLA-B*5701 status who have previously
88 tolerated abacavir. For HLA-B*5701-positive patients, treatment with an abacavir-containing
89 regimen is not recommended and should be considered only with close medical supervision and
90 under exceptional circumstances when the potential benefit outweighs the risk.

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

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

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

100 Group 1: Fever

101 Group 2: Rash

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

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

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

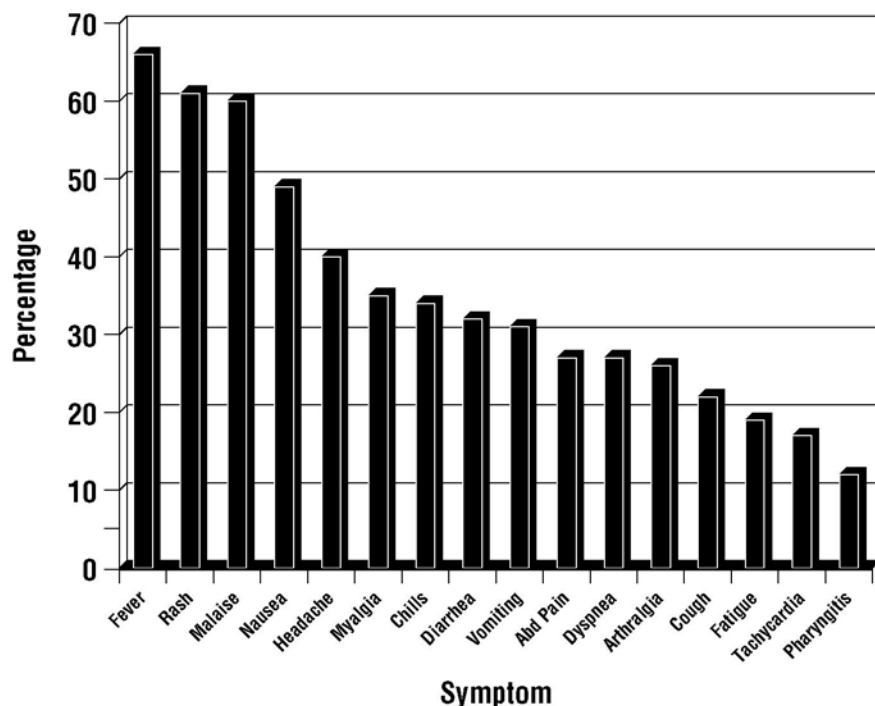
105 Hypersensitivity to abacavir following the presentation of a single sign or symptom has
106 been reported infrequently.

107 Hypersensitivity to abacavir was reported in approximately 8% of 2,670 subjects
108 (n = 206) in 9 clinical studies (range: 2% to 9%) with enrollment from November 1999 to
109 February 2002. Data on time to onset and symptoms of suspected hypersensitivity were collected
110 on a detailed data collection module. The frequencies of symptoms are shown in Figure 1.
111 Symptoms usually appeared within the first 6 weeks of treatment with abacavir, although the
112 reaction may occur at any time during therapy. Median time to onset was 9 days; 89% appeared

113 within the first 6 weeks; 95% of subjects reported symptoms from 2 or more of the 5 groups
114 listed above.

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116 **Figure 1: Hypersensitivity-Related Symptoms Reported With**
117 **≥10% Frequency in Clinical Studies (n = 206 Subjects)**



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120 Other less common signs and symptoms of hypersensitivity include lethargy, myolysis,
121 edema, abnormal chest x-ray findings (predominantly infiltrates, which can be localized), and
122 paresthesia. Anaphylaxis, liver failure, renal failure, hypotension, adult respiratory distress
123 syndrome, respiratory failure, and death have occurred in association with hypersensitivity
124 reactions. In one study, 4 subjects (11%) receiving ZIAGEN 600 mg once daily experienced
125 hypotension with a hypersensitivity reaction compared with 0 subjects receiving ZIAGEN
126 300 mg twice daily.

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

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

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

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

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

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

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

153 If symptoms consistent with hypersensitivity are not identified, reintroduction can be
154 undertaken with continued monitoring for symptoms of a hypersensitivity reaction. Make
155 patients aware that a hypersensitivity reaction can occur with reintroduction of EPZICOM or any
156 other abacavir-containing product and that reintroduction of EPZICOM or introduction of any
157 other abacavir-containing product needs to be undertaken only if medical care can be readily
158 accessed by the patient or others.

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

161 CNA106030 (PREDICT-1), a randomized, double-blind study, evaluated the clinical
162 utility of prospective HLA-B*5701 screening on the incidence of abacavir hypersensitivity
163 reaction in abacavir-naive HIV-1-infected adults (n = 1,650). In this study, use of pre-therapy
164 screening for the HLA-B*5701 allele and exclusion of subjects with this allele reduced the
165 incidence of clinically suspected abacavir hypersensitivity reactions from 7.8% (66/847) to 3.4%
166 (27/803). Based on this study, it is estimated that 61% of patients with the HLA-B*5701 allele
167 will develop a clinically suspected hypersensitivity reaction during the course of abacavir
168 treatment compared with 4% of patients who do not have the HLA-B*5701 allele.

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

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

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

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

185 **5.2 Lactic Acidosis and Severe Hepatomegaly With Steatosis**

186 Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been
187 reported with the use of nucleoside analogues alone or in combination, including abacavir and
188 lamivudine and other antiretrovirals. A majority of these cases have been in women. Obesity and
189 prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when
190 administering EPZICOM to any patient with known risk factors for liver disease; however, cases
191 have also been reported in patients with no known risk factors. Treatment with EPZICOM
192 should be suspended in any patient who develops clinical or laboratory findings suggestive of
193 lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis
194 even in the absence of marked transaminase elevations).

195 **5.3 Patients With HIV-1 and Hepatitis B Virus Co-Infection**

196 Posttreatment Exacerbations of Hepatitis: In clinical studies in non-HIV-1-infected
197 subjects treated with lamivudine for chronic HBV, clinical and laboratory evidence of
198 exacerbations of hepatitis have occurred after discontinuation of lamivudine. These
199 exacerbations have been detected primarily by serum ALT elevations in addition to
200 re-emergence of HBV DNA. Although most events appear to have been self-limited, fatalities
201 have been reported in some cases. Similar events have been reported from post-marketing
202 experience after changes from lamivudine-containing HIV-1 treatment regimens to
203 non-lamivudine-containing regimens in patients infected with both HIV-1 and HBV. The causal
204 relationship to discontinuation of lamivudine treatment is unknown. Patients should be closely
205 monitored with both clinical and laboratory follow-up for at least several months after stopping
206 treatment. There is insufficient evidence to determine whether re-initiation of lamivudine alters
207 the course of posttreatment exacerbations of hepatitis.

208 Emergence of Lamivudine-Resistant HBV: Safety and efficacy of lamivudine have
209 not been established for treatment of chronic hepatitis B in subjects dually infected with HIV-1
210 and HBV. In non-HIV-1-infected subjects treated with lamivudine for chronic hepatitis B,
211 emergence of lamivudine-resistant HBV has been detected and has been associated with
212 diminished treatment response (see full prescribing information for EPIVIR-HBV® [lamivudine]
213 Tablets and Oral Solution for additional information). Emergence of hepatitis B virus variants
214 associated with resistance to lamivudine has also been reported in HIV-1-infected subjects who
215 have received lamivudine-containing antiretroviral regimens in the presence of concurrent
216 infection with hepatitis B virus.

217 **5.4 Use With Interferon- and Ribavirin-Based Regimens**

218 In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine
219 nucleoside analogues such as lamivudine, a component of EPZICOM. Although no evidence of a
220 pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic
221 suppression) was seen when ribavirin was coadministered with lamivudine in HIV-1/HCV
222 co-infected subjects [see *Clinical Pharmacology (12.3)*], hepatic decompensation (some fatal)
223 has occurred in HIV-1/HCV co-infected subjects receiving combination antiretroviral therapy for
224 HIV-1 and interferon alfa with or without ribavirin. Patients receiving interferon alfa with or
225 without ribavirin and EPZICOM should be closely monitored for treatment-associated toxicities,
226 especially hepatic decompensation. Discontinuation of EPZICOM should be considered as
227 medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both
228 should also be considered if worsening clinical toxicities are observed, including hepatic
229 decompensation (e.g., Child-Pugh >6) (see the complete prescribing information for interferon
230 and ribavirin).

231 **5.5 Immune Reconstitution Syndrome**

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

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

241 **5.6 Fat Redistribution**

242 Redistribution/accumulation of body fat including central obesity, dorsocervical fat
243 enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and
244 "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The
245 mechanism and long-term consequences of these events are currently unknown. A causal
246 relationship has not been established.

247 **5.7 Myocardial Infarction**

248 In a published prospective, observational, epidemiological study designed to investigate
249 the rate of myocardial infarction in patients on combination antiretroviral therapy, the use of
250 abacavir within the previous 6 months was correlated with an increased risk of myocardial
251 infarction (MI).¹ In a sponsor-conducted pooled analysis of clinical studies, no excess risk of MI
252 was observed in abacavir-treated subjects as compared with control subjects. In totality, the
253 available data from the observational cohort and from clinical studies are inconclusive.

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

257 **5.8 Use With Other Abacavir-, Lamivudine-, and/or Emtricitabine-Containing**
258 **Products**

259 EPZICOM contains fixed doses of 2 nucleoside analogues, abacavir and lamivudine, and
260 should not be administered concomitantly with other abacavir-containing and/or
261 lamivudine-containing products, including ZIAGEN (abacavir sulfate) Tablets and Oral
262 Solution, EPIVIR (lamivudine) Tablets and Oral Solution, EPIVIR-HBV[®] (lamivudine) Tablets
263 and Oral Solution, COMBIVIR[®] (lamivudine and zidovudine) Tablets, or TRIZIVIR[®] (abacavir
264 sulfate, lamivudine, and zidovudine) Tablets; or emtricitabine-containing products, including
265 ATRIPLA[®] (efavirenz/emtricitabine/tenofovir disoproxil fumarate) Tablets, EMTRIVA[®]
266 (emtricitabine) Capsules and Oral Solution, TRUVADA[®] (emtricitabine/tenofovir disoproxil
267 fumarate) Tablets, or COMPLERA[™] (emtricitabine/rilpivirine/tenofovir disoproxil fumarate)
268 Tablets.

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

271 **6 ADVERSE REACTIONS**

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

- 274 • Serious and sometimes fatal hypersensitivity reaction. In one study, once-daily dosing of
275 abacavir was associated with more severe hypersensitivity reactions [*see Boxed Warning,*
276 *Warnings and Precautions (5.1)*].
- 277 • Lactic acidosis and severe hepatomegaly [*see Boxed Warning, Warnings and Precautions*
278 *(5.2)*].
- 279 • Acute exacerbations of hepatitis B [*see Boxed Warning, Warnings and Precautions (5.3)*].
- 280 • Hepatic decompensation in patients co-infected with HIV-1 and Hepatitis C [*see Warnings*
281 *and Precautions (5.4)*].
- 282 • Immune reconstitution syndrome [*see Warnings and Precautions (5.5)*].
- 283 • Fat redistribution [*see Warnings and Precautions (5.6)*].
- 284 • Myocardial infarction [*see Warnings and Precautions (5.7)*].

285 **6.1 Clinical Trials Experience**

286 Because clinical studies are conducted under widely varying conditions, adverse reaction
287 rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical
288 studies of another drug and may not reflect the rates observed in clinical practice.

289 Therapy-Naive Adults: Treatment-emergent clinical adverse reactions (rated by the
290 investigator as moderate or severe) with a $\geq 5\%$ frequency during therapy with ZIAGEN 600 mg
291 once daily or ZIAGEN 300 mg twice daily, both in combination with lamivudine 300 mg once
292 daily and efavirenz 600 mg once daily are listed in Table 1.

293

294 **Table 1. Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate**
 295 **Intensity (Grades 2-4, ≥5% Frequency) in Therapy-Naive Adults (CNA30021) Through**
 296 **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)
Drug hypersensitivity^{a,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 ^a	5%	6%
Rash	5%	5%
Pyrexia	5%	3%
Abdominal pain/gastritis	4%	5%
Abnormal dreams	4%	5%
Anxiety	3%	5%

297 ^a Subjects receiving ZIAGEN 600 mg once daily, experienced a significantly higher incidence
 298 of severe drug hypersensitivity reactions and severe diarrhea compared with subjects who
 299 received ZIAGEN 300 mg twice daily. Five percent (5%) of subjects receiving ZIAGEN
 300 600 mg once daily had severe drug hypersensitivity reactions compared with 2% of subjects
 301 receiving ZIAGEN 300 mg twice daily. Two percent (2%) of subjects receiving ZIAGEN
 302 600 mg once daily had severe diarrhea while none of the subjects receiving ZIAGEN 300 mg
 303 twice daily had this event.

304 ^b Study CNA30024 was a multi-center, double-blind, controlled study in which
 305 649 HIV-1-infected, therapy-naive adults were randomized and received either ZIAGEN
 306 (300 mg twice daily), EPIVIR (150 mg twice daily), and efavirenz (600 mg once daily) or
 307 zidovudine (300 mg twice daily), EPIVIR (150 mg twice daily), and efavirenz (600 mg once
 308 daily). CNA30024 used double-blind ascertainment of suspected hypersensitivity reactions.
 309 During the blinded portion of the study, suspected hypersensitivity to abacavir was reported
 310 by investigators in 9% of 324 subjects in the abacavir group and 3% of 325 subjects in the
 311 zidovudine group.

312
 313 **Laboratory Abnormalities:** Laboratory abnormalities observed in clinical studies of
 314 ZIAGEN were anemia, neutropenia, liver function test abnormalities, and elevations of CPK,
 315 blood glucose, and triglycerides. Additional laboratory abnormalities observed in clinical studies
 316 of EPIVIR were thrombocytopenia and elevated levels of bilirubin, amylase, and lipase.

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

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

322 **6.2 Postmarketing Experience**

323 In addition to adverse reactions reported from clinical studies, the following reactions
324 have been identified during postmarketing use of abacavir, lamivudine, and/or EPZICOM.
325 Because they are reported voluntarily from a population of unknown size, estimates of frequency
326 cannot be made. These reactions have been chosen for inclusion due to a combination of their
327 seriousness, frequency of reporting, or potential causal connection to abacavir, lamivudine,
328 and/or EPZICOM.

329 Abacavir:

330 *Cardiovascular:* Myocardial infarction.

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

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

338 Abacavir and Lamivudine:

339 *Body as a Whole:* Redistribution/accumulation of body fat [*see Warnings and*
340 *Precautions (5.6)*].

341 *Digestive:* Stomatitis.

342 *Endocrine and Metabolic:* Hyperglycemia.

343 *General:* Weakness.

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

346 *Hepatic:* Lactic acidosis and hepatic steatosis [*see Warnings and Precautions (5.2)*],
347 posttreatment exacerbation of hepatitis B [*see Warnings and Precautions (5.3)*].

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

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

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

351 *Respiratory:* Abnormal breath sounds/wheezing.

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

353 **7 DRUG INTERACTIONS**

- 354 • No drug interaction studies have been conducted using EPZICOM Tablets [*see Clinical*
355 *Pharmacology (12.3)*].

356 **7.1 Ethanol**

357 Abacavir: Abacavir has no effect on the pharmacokinetic properties of ethanol. Ethanol
358 decreases the elimination of abacavir causing an increase in overall exposure [see *Clinical*
359 *Pharmacology (12.3)*].

360 **7.2 Interferon- and Ribavirin-Based Regimens**

361 Lamivudine: Although no evidence of a pharmacokinetic or pharmacodynamic
362 interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was
363 coadministered with lamivudine in HIV-1/HCV co-infected subjects, hepatic decompensation
364 (some fatal) has occurred in HIV-1/HCV co-infected subjects receiving combination
365 antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin [see *Warnings and*
366 *Precautions (5.4), Clinical Pharmacology (12.3)*].

367 **7.3 Methadone**

368 Abacavir: The addition of methadone has no clinically significant effect on the
369 pharmacokinetic properties of abacavir. In a study of 11 HIV-1-infected subjects receiving
370 methadone-maintenance therapy with 600 mg of ZIAGEN twice daily (twice the currently
371 recommended dose), oral methadone clearance increased [see *Clinical Pharmacology (12.3)*].
372 This alteration will not result in a methadone dose modification in the majority of patients;
373 however, an increased methadone dose may be required in a small number of patients.

374 **7.4 Trimethoprim/Sulfamethoxazole (TMP/SMX)**

375 Lamivudine: No change in dose of either drug is recommended [see *Clinical*
376 *Pharmacology (12.3)*]. There is no information regarding the effect on lamivudine
377 pharmacokinetics of higher doses of TMP/SMX such as those used to treat PCP.

378 **8 USE IN SPECIFIC POPULATIONS**

379 **8.1 Pregnancy**

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

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

393 Lamivudine: Studies in pregnant rats showed that lamivudine is transferred to the fetus
394 through the placenta. Reproduction studies with orally administered lamivudine have been

395 performed in rats and rabbits at doses producing plasma levels up to approximately 35 times that
396 for the recommended adult HIV dose. No evidence of teratogenicity due to lamivudine was
397 observed. Evidence of early embryoletality was seen in the rabbit at exposure levels similar to
398 those observed in humans, but there was no indication of this effect in the rat at exposure levels
399 up to 35 times those in humans.

400 Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant
401 women exposed to EPZICOM or other antiretroviral agents, an Antiretroviral Pregnancy
402 Registry has been established. Physicians are encouraged to register patients by calling 1-800-
403 258-4263.

404 **8.3 Nursing Mothers**

405 The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers
406 not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection.

407 Abacavir: Abacavir is secreted into the milk of lactating rats.

408 Lamivudine: Lamivudine is excreted in human breast milk and into the milk of lactating
409 rats.

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

413 **8.4 Pediatric Use**

414 Safety and effectiveness of EPZICOM in pediatric patients have not been established.
415 EPZICOM is not recommended for use in patients aged <18 years because it cannot be dose
416 adjusted.

417 **8.5 Geriatric Use**

418 Clinical studies of abacavir and lamivudine did not include sufficient numbers of subjects
419 aged 65 and over to determine whether they respond differently from younger subjects. In
420 general, dose selection for an elderly patient should be cautious, reflecting the greater frequency
421 of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy
422 [*see Dosage and Administration (2.2), Use in Specific Populations (8.6, 8.7)*].

423 **8.6 Patients With Impaired Renal Function**

424 EPZICOM is not recommended for patients with impaired renal function (creatinine
425 clearance <50 mL/min) because EPZICOM is a fixed-dose combination and the dosage of the
426 individual components cannot be adjusted.

427 **8.7 Patients With Impaired Hepatic Function**

428 EPZICOM is contraindicated for patients with hepatic impairment because EPZICOM is
429 a fixed-dose combination and the dosage of the individual components cannot be adjusted.

430 **10 OVERDOSAGE**

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

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

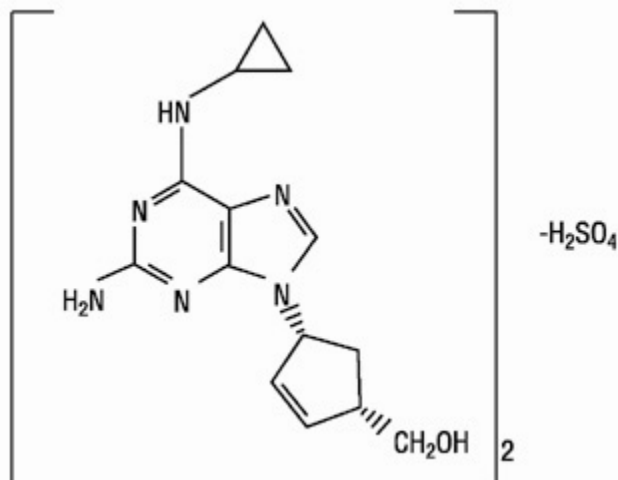
436 11 DESCRIPTION

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

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

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

450

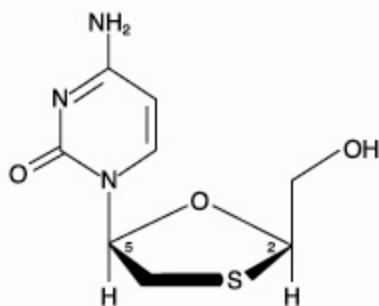


452

453 Abacavir sulfate is a white to off-white solid with a solubility of approximately
454 77 mg/mL in distilled water at 25°C.

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

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



462
463 Lamivudine is a white to off-white crystalline solid with a solubility of approximately
464 70 mg/mL in water at 20°C.

465 12 CLINICAL PHARMACOLOGY

466 12.1 Mechanism of Action

467 EPZICOM is an antiviral agent [see *Clinical Pharmacology (12.4)*].

468 12.3 Pharmacokinetics

469 Pharmacokinetics in Adults: EPZICOM: In a single-dose, 3-way crossover
470 bioavailability study of 1 EPZICOM Tablet versus 2 ZIAGEN Tablets (2 x 300 mg) and
471 2 EPIVIR Tablets (2 x 150 mg) administered simultaneously in healthy subjects (n = 25), there
472 was no difference in the extent of absorption, as measured by the area under the plasma
473 concentration-time curve (AUC) and maximal peak concentration (C_{max}), of each component.

474 Abacavir: Following oral administration, abacavir is rapidly absorbed and extensively
475 distributed. After oral administration of a single dose of 600 mg of abacavir in 20 subjects, C_{max}
476 was 4.26 ± 1.19 mcg/mL (mean \pm SD) and AUC_{∞} was 11.95 ± 2.51 mcg•hr/mL. Binding of
477 abacavir to human plasma proteins is approximately 50% and was independent of concentration.
478 Total blood and plasma drug-related radioactivity concentrations are identical, demonstrating
479 that abacavir readily distributes into erythrocytes. The primary routes of elimination of abacavir
480 are metabolism by alcohol dehydrogenase to form the 5'-carboxylic acid and glucuronyl
481 transferase to form the 5'-glucuronide.

482 Lamivudine: Following oral administration, lamivudine is rapidly absorbed and
483 extensively distributed. After multiple-dose oral administration of lamivudine 300 mg once daily
484 for 7 days to 60 healthy volunteers, steady-state C_{max} ($C_{max,ss}$) was 2.04 ± 0.54 mcg/mL
485 (mean \pm SD) and the 24-hour steady-state AUC ($AUC_{24,ss}$) was 8.87 ± 1.83 mcg•hr/mL. Binding
486 to plasma protein is low. Approximately 70% of an intravenous dose of lamivudine is recovered
487 as unchanged drug in the urine. Metabolism of lamivudine is a minor route of elimination. In
488 humans, the only known metabolite is the trans-sulfoxide metabolite (approximately 5% of an
489 oral dose after 12 hours).

490 The steady-state pharmacokinetic properties of the EPIVIR 300-mg tablet once daily for
491 7 days compared with the EPIVIR 150-mg tablet twice daily for 7 days were assessed in a

492 crossover study in 60 healthy volunteers. EPIVIR 300 mg once daily resulted in lamivudine
 493 exposures that were similar to EPIVIR 150 mg twice daily with respect to plasma AUC_{24,ss};
 494 however, C_{max,ss} was 66% higher and the trough value was 53% lower compared with the
 495 150-mg twice-daily regimen. Intracellular lamivudine triphosphate exposures in peripheral blood
 496 mononuclear cells were also similar with respect to AUC_{24,ss} and C_{max24,ss}; however, trough
 497 values were lower compared with the 150-mg twice-daily regimen. Inter-subject variability was
 498 greater for intracellular lamivudine triphosphate concentrations versus lamivudine plasma trough
 499 concentrations. The clinical significance of observed differences for both plasma lamivudine
 500 concentrations and intracellular lamivudine triphosphate concentrations is not known.

501 In humans, abacavir and lamivudine are not significantly metabolized by cytochrome
 502 P450 enzymes.

503 The pharmacokinetic properties of abacavir and lamivudine in fasting subjects are
 504 summarized in Table 2.

505

506 **Table 2. Pharmacokinetic Parameters^a 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 ^b	

507 ^a Data presented as mean ± standard deviation except where noted.

508 ^b Approximate range.

509

510 **Effect of Food on Absorption of EPZICOM:** EPZICOM may be administered with or
 511 without food. Administration with a high-fat meal in a single-dose bioavailability study resulted
 512 in no change in AUC_{last}, AUC_∞, and C_{max} for lamivudine. Food did not alter the extent of
 513 systemic exposure to abacavir (AUC_∞), but the rate of absorption (C_{max}) was decreased
 514 approximately 24% compared with fasted conditions (n = 25). These results are similar to those
 515 from previous studies of the effect of food on abacavir and lamivudine tablets administered
 516 separately.

517 **Special Populations: Renal Impairment: EPZICOM:** Because lamivudine requires
 518 dose adjustment in the presence of renal insufficiency, EPZICOM is not recommended for use in
 519 patients with creatinine clearance <50 mL/min [see *Dosage and Administration (2.2)*].

520 **Hepatic Impairment: EPZICOM:** EPZICOM is contraindicated for patients with
 521 hepatic impairment because EPZICOM is a fixed-dose combination and the dosage of the
 522 individual components cannot be adjusted. Abacavir is contraindicated in patients with moderate
 523 to severe hepatic impairment, and dose reduction is required in patients with mild hepatic
 524 impairment.

525 **Pregnancy:** See *Use in Specific Populations (8.1)*.

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

528 *Nursing Mothers:* See *Use in Specific Populations (8.3)*.

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

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

534 *Pediatric Patients: EPZICOM:* The pharmacokinetics of EPZICOM in pediatric
535 subjects are under investigation. There are insufficient data at this time to recommend a dose.

536 *Geriatric Patients:* The pharmacokinetics of abacavir and lamivudine have not been
537 studied in subjects over 65 years of age.

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

541 *Lamivudine:* A pharmacokinetic study in healthy male (n = 12) and female
542 (n = 12) subjects showed no gender differences in lamivudine AUC_∞ normalized for body
543 weight.

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

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

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

553 *Abacavir: Lamivudine and Zidovudine:* Fifteen HIV-1-infected subjects were
554 enrolled in a crossover-designed drug interaction study evaluating single doses of abacavir
555 (600 mg), lamivudine (150 mg), and zidovudine (300 mg) alone or in combination. Analysis
556 showed no clinically relevant changes in the pharmacokinetics of abacavir with the addition of
557 lamivudine or zidovudine or the combination of lamivudine and zidovudine. Lamivudine
558 exposure (AUC decreased 15%) and zidovudine exposure (AUC increased 10%) did not show
559 clinically relevant changes with concurrent abacavir.

560 *Methadone:* In a study of 11 HIV-1-infected subjects receiving
561 methadone-maintenance therapy (40 mg and 90 mg daily), with 600 mg of ZIAGEN twice daily
562 (twice the currently recommended dose), oral methadone clearance increased 22% (90% CI: 6%
563 to 42%) [*see Drug Interactions (7.4)*].

564 *Lamivudine: Zidovudine:* No clinically significant alterations in lamivudine or
565 zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-1-infected adult subjects

566 given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine
 567 (300 mg q 12 hr).

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

574 The effects of other coadministered drugs on abacavir or lamivudine are provided in
 575 Table 3.

577 **Table 3. 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%	↔

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

580

581 12.4 Microbiology

582 Mechanism of Action: *Abacavir:* Abacavir is a carbocyclic synthetic nucleoside
 583 analogue. Abacavir is converted by cellular enzymes to the active metabolite, carbovir
 584 triphosphate (CBV-TP), an analogue of deoxyguanosine-5'-triphosphate (dGTP). CBV-TP
 585 inhibits the activity of HIV-1 reverse transcriptase (RT) both by competing with the natural
 586 substrate dGTP and by its incorporation into viral DNA. The lack of a 3'-OH group in the

587 incorporated nucleotide analogue prevents the formation of the 5' to 3' phosphodiester linkage
588 essential for DNA chain elongation, and therefore, the viral DNA growth is terminated. CBV-TP
589 is a weak inhibitor of cellular DNA polymerases α , β , and γ .

590 **Lamivudine:** Lamivudine is a synthetic nucleoside analogue. Intracellularly
591 lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate
592 (3TC-TP). The principal mode of action of 3TC-TP is inhibition of RT via DNA chain
593 termination after incorporation of the nucleotide analogue. CBV-TP and 3TC-TP are weak
594 inhibitors of cellular DNA polymerases α , β , and γ .

595 **Antiviral Activity: Abacavir:** The antiviral activity of abacavir against HIV-1 was
596 evaluated against a T-cell tropic laboratory strain HIV-1_{IIIB} in lymphoblastic cell lines, a
597 monocyte/macrophage tropic laboratory strain HIV-1_{BaL} in primary monocytes/macrophages,
598 and clinical isolates in peripheral blood mononuclear cells. The concentration of drug necessary
599 to effect viral replication by 50 percent (EC_{50}) ranged from 3.7 to 5.8 μM
600 (1 μM = 0.28 mcg/mL) and 0.07 to 1.0 μM against HIV-1_{IIIB} and HIV-1_{BaL}, respectively, and
601 was $0.26 \pm 0.18 \mu\text{M}$ against 8 clinical isolates. The EC_{50} values of abacavir against different
602 HIV-1 clades (A-G) ranged from 0.0015 to 1.05 μM , and against HIV-2 isolates, from 0.024 to
603 0.49 μM . Ribavirin (50 μM) had no effect on the anti-HIV-1 activity of abacavir in cell culture.

604 **Lamivudine:** The antiviral activity of lamivudine against HIV-1 was assessed in a
605 number of cell lines (including monocytes and fresh human peripheral blood lymphocytes) using
606 standard susceptibility assays. EC_{50} values were in the range of 0.003 to 15 μM
607 (1 μM = 0.23 mcg/mL). HIV-1 from therapy-naive subjects with no amino acid substitutions
608 associated with resistance gave median EC_{50} values of 0.429 μM (range: 0.200 to 2.007 μM)
609 from Virco (n = 92 baseline samples from COLA40263) and 2.35 μM (1.37 to 3.68 μM) from
610 Monogram Biosciences (n = 135 baseline samples from ESS30009). The EC_{50} values of
611 lamivudine against different HIV-1 clades (A-G) ranged from 0.001 to 0.120 μM , and against
612 HIV-2 isolates from 0.003 to 0.120 μM in peripheral blood mononuclear cells. Ribavirin
613 (50 μM) decreased the anti-HIV-1 activity of lamivudine by 3.5 fold in MT-4 cells.

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

623 **Resistance:** HIV-1 isolates with reduced susceptibility to the combination of abacavir
624 and lamivudine have been selected in cell culture and have also been obtained from subjects
625 failing abacavir/lamivudine-containing regimens. Genotypic characterization of

626 abacavir/lamivudine-resistant viruses selected in cell culture identified amino acid substitutions
627 M184V/I, K65R, L74V, and Y115F in HIV-1 RT.

628 Genotypic analysis of isolates selected in cell culture and recovered from abacavir-treated
629 subjects demonstrated that amino acid substitutions K65R, L74V, Y115F, and M184V/I in
630 HIV-1 RT contributed to abacavir resistance. Genotypic analysis of isolates selected in cell
631 culture and recovered from lamivudine-treated subjects showed that the resistance was due to a
632 specific amino acid substitution in HIV-1 RT at codon 184 changing the methionine to either
633 isoleucine or valine (M184V/I). In a study of therapy-naïve adults receiving ZIAGEN 600 mg
634 once daily (n = 384) or 300 mg twice daily (n = 386) in a background regimen of lamivudine
635 300 mg and efavirenz 600 mg once daily (Study CNA30021), the incidence of virologic failure
636 at 48 weeks was similar between the 2 groups (11% in both arms). Genotypic (n = 38) and
637 phenotypic analyses (n = 35) of virologic failure isolates from this study showed that the RT
638 substitutions that emerged during abacavir/lamivudine once-daily and twice-daily therapy were
639 K65R, L74V, Y115F, and M184V/I. The abacavir- and lamivudine-associated resistance
640 substitution M184V/I was the most commonly observed substitution in virologic failure isolates
641 from subjects receiving abacavir/lamivudine once daily (56%, 10/18) and twice daily (40%,
642 8/20).

643 Thirty-nine percent (7/18) of the isolates from subjects who experienced virologic failure
644 in the abacavir once-daily arm had a >2.5-fold decrease in abacavir susceptibility with a
645 median-fold decrease of 1.3 (range: 0.5 to 11) compared with 29% (5/17) of the failure isolates
646 in the twice-daily arm with a median-fold decrease of 0.92 (range: 0.7 to 13). Fifty-six percent
647 (10/18) of the virologic failure isolates in the once-daily abacavir group compared with 41%
648 (7/17) of the failure isolates in the twice-daily abacavir group had a >2.5-fold decrease in
649 lamivudine susceptibility with median-fold changes of 81 (range: 0.79 to >116) and 1.1 (range:
650 0.68 to >116) in the once-daily and twice-daily abacavir arms, respectively.

651 **Cross-Resistance:** Cross-resistance has been observed among NRTIs. Viruses
652 containing abacavir and lamivudine resistance-associated amino acid substitutions, namely,
653 K65R, L74V, M184V, and Y115F, exhibit cross-resistance to didanosine, emtricitabine,
654 lamivudine, tenofovir, and zalcitabine in cell culture and in subjects. The K65R substitution can
655 confer resistance to abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and
656 zalcitabine; the L74V substitution can confer resistance to abacavir, didanosine, and zalcitabine;
657 and the M184V substitution can confer resistance to abacavir, didanosine, emtricitabine,
658 lamivudine, and zalcitabine.

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

664 **13 NONCLINICAL TOXICOLOGY**

665 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

666 Carcinogenicity: Abacavir: Abacavir was administered orally at 3 dosage levels to
667 separate groups of mice and rats in 2-year carcinogenicity studies. Results showed an increase in
668 the incidence of malignant and non-malignant tumors. Malignant tumors occurred in the
669 preputial gland of males and the clitoral gland of females of both species, and in the liver of
670 female rats. In addition, non-malignant tumors also occurred in the liver and thyroid gland of
671 female rats. These observations were made at systemic exposures in the range of 6 to 32 times
672 the human exposure at the recommended dose.

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

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

678 Mutagenicity: Abacavir: Abacavir induced chromosomal aberrations both in the
679 presence and absence of metabolic activation in an in vitro cytogenetic study in human
680 lymphocytes. Abacavir was mutagenic in the absence of metabolic activation, although it was
681 not mutagenic in the presence of metabolic activation in an L5178Y mouse lymphoma assay.
682 Abacavir was clastogenic in males and not clastogenic in females in an in vivo mouse bone
683 marrow micronucleus assay. Abacavir was not mutagenic in bacterial mutagenicity assays in the
684 presence and absence of metabolic activation.

685 Lamivudine: Lamivudine was mutagenic in an L5178Y mouse lymphoma assay and
686 clastogenic in a cytogenetic assay using cultured human lymphocytes. Lamivudine was not
687 mutagenic in a microbial mutagenicity assay, in an in vitro cell transformation assay, in a rat
688 micronucleus test, in a rat bone marrow cytogenetic assay, and in an assay for unscheduled DNA
689 synthesis in rat liver.

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

694 **13.2 Animal Toxicology and/or Pharmacology**

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

698 **14 CLINICAL STUDIES**

699 EPZICOM: There have been no clinical studies conducted with EPZICOM. One
700 EPZICOM Tablet given once daily is an alternative regimen to EPIVIR Tablets 300 mg once
701 daily plus ZIAGEN Tablets 2 x 300 mg once daily as a component of antiretroviral therapy.

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

703 Therapy-Naive Adults: CNA30021 was an international, multi-center, double-blind,
 704 controlled study in which 770 HIV-1-infected, therapy-naive adults were randomized and
 705 received either ZIAGEN 600 mg once daily or ZIAGEN 300 mg twice daily, both in
 706 combination with EPIVIR 300 mg once daily and efavirenz 600 mg once daily. The double-blind
 707 treatment duration was at least 48 weeks. Study participants had a mean age of 37 years, were:
 708 male (81%), Caucasian (54%), black (27%), and American Hispanic (15%). The median baseline
 709 CD4+ cell count was 262 cells/mm³ (range: 21 to 918 cells/mm³) and the median baseline
 710 plasma HIV-1 RNA was 4.89 log₁₀ copies/mL (range: 2.60 to 6.99 log₁₀ copies/mL).

711 The outcomes of randomized treatment are provided in Table 4.
 712

713 **Table 4. 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 ^a	64% (71%)	65% (72%)
Virologic failure ^b	11% (5%)	11% (5%)
Discontinued due to adverse reactions	13%	11%
Discontinued due to other reasons ^c	11%	13%

714 ^a Subjects achieved and maintained confirmed HIV-1 RNA <50 copies/mL (<400 copies/mL)
 715 through Week 48 (Roche AMPLICOR Ultrasensitive HIV-1 MONITOR[®] standard test
 716 version 1.0).

717 ^b Includes viral rebound, failure to achieve confirmed <50 copies/mL (<400 copies/mL) by
 718 Week 48, and insufficient viral load response.

719 ^c Includes consent withdrawn, lost to follow-up, protocol violations, clinical progression, and
 720 other.

721
 722 After 48 weeks of therapy, the median CD4+ cell count increases from baseline were
 723 188 cells/mm³ in the group receiving ZIAGEN 600 mg once daily and 200 cells/mm³ in the
 724 group receiving ZIAGEN 300 mg twice daily. Through Week 48, 6 subjects (2%) in the group
 725 receiving ZIAGEN 600 mg once daily (4 CDC classification C events and 2 deaths) and
 726 10 subjects (3%) in the group receiving ZIAGEN 300 mg twice daily (7 CDC classification C
 727 events and 3 deaths) experienced clinical disease progression. None of the deaths were attributed
 728 to study medications.

729 **15 REFERENCES**

730 1. Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study Group. *Lancet*.
 731 2008;371 (9622):1417-1426.

732 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

737 Bottles of 30 Tablets (NDC 49702-206-13).

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

740 **17 PATIENT COUNSELING INFORMATION**

741 See FDA-approved patient labeling (Medication Guide)

742 Hypersensitivity Reaction: Inform patients:

- 743 • that a Medication Guide and Warning Card summarizing the symptoms of the abacavir
744 hypersensitivity reaction and other product information will be dispensed by the pharmacist
745 with each new prescription and refill of EPZICOM, and encourage the patient to read the
746 Medication Guide and Warning Card every time to obtain any new information that may be
747 present about EPZICOM. (The complete text of the Medication Guide is reprinted at the end
748 of this document.)
- 749 • to carry the Warning Card with them.
- 750 • how to identify a hypersensitivity reaction [*see Warnings and Precautions (5.1), Medication*
751 *Guide*].
- 752 • that if they develop symptoms consistent with a hypersensitivity reaction they should call
753 their doctor right away to determine if they should stop taking EPZICOM.
- 754 • that a hypersensitivity reaction can worsen and lead to hospitalization or death if EPZICOM
755 is not immediately discontinued.
- 756 • that in one study, more severe hypersensitivity reactions were seen when ZIAGEN was dosed
757 600 mg once daily.
- 758 • to not restart EPZICOM or any other abacavir-containing product following a
759 hypersensitivity reaction because more severe symptoms can occur within hours and may
760 include life-threatening hypotension and death.
- 761 • that a hypersensitivity reaction is usually reversible if it is detected promptly and EPZICOM
762 is stopped right away.
- 763 • that if they have interrupted EPZICOM for reasons other than symptoms of hypersensitivity
764 (for example, those who have an interruption in drug supply), a serious or fatal
765 hypersensitivity reaction may occur with reintroduction of abacavir.
- 766 • to not restart EPZICOM or any other abacavir-containing product without medical
767 consultation and that restarting abacavir needs to be undertaken only if medical care can be
768 readily accessed by the patient or others.
- 769 • EPZICOM should not be administered concomitantly with ATRIPLA, COMBIVIR,
770 COMPLERA, EMTRIVA, EPIVIR, EPIVIR-HBV, TRIZIVIR, TRUVADA, or ZIAGEN.

771 Lactic Acidosis/Hepatomegaly: Inform patients that some HIV medicines, including
772 EPZICOM, can cause a rare, but serious condition called lactic acidosis with liver
773 enlargement (hepatomegaly) [see *Warnings and Precautions (5.2)*].

774 HIV-1/ HBV Co-infection: Patients co-infected with HIV-1 and HBV should be
775 informed that deterioration of liver disease has occurred in some cases when treatment with
776 lamivudine was discontinued. Patients should be advised to discuss any changes in regimen with
777 their physician [see *Warnings and Precautions (5.3)*].

778 HIV-1/HCV Co-Infection: Patients with HIV-1/HCV co-infection should be informed
779 that hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients
780 receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without
781 ribavirin [see *Warnings and Precautions (5.4)*].

782 Redistribution/Accumulation of Body Fat: Inform patients that redistribution or
783 accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause
784 and long-term health effects of these conditions are not known at this time [see *Warnings and*
785 *Precautions (5.6)*].

786 Information About HIV-1 Infection: EPZICOM is not a cure for HIV-1 infection and
787 patients may continue to experience illnesses associated with HIV-1 infection, including
788 opportunistic infections. Patients should remain under the care of a physician when using
789 EPZICOM.

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

- 792 • **Do not share needles or other injection equipment.**
- 793 • **Do not share personal items that can have blood or body fluids on them, like**
794 **toothbrushes and razor blades.**
- 795 • **Do not have any kind of sex without protection.** Always practice safe sex by using a
796 latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal
797 secretions, or blood.
- 798 • **Do not breastfeed.** Lamivudine is excreted in human breast milk. It is not known if
799 abacavir can be passed to your baby in your breast milk and whether it could harm your
800 baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to
801 the baby in the breast milk.

802 Patients should be informed to take all HIV medications exactly as prescribed.

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809 Healthcare or its products.

810

811 Manufactured for



812 ViiV Healthcare
813 Research Triangle Park, NC 27709

814 by:



816 GlaxoSmithKline
817 Research Triangle Park, NC 27709

818 Lamivudine is manufactured under agreement from
819 **Shire Pharmaceuticals Group plc**

820 Basingstoke, UK

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822 EPZ:PI

827

MEDICATION GUIDE

829 **EPZICOM[®] (ep' zih com)**
830 (abacavir sulfate and lamivudine)

Tablets

832

833 Read this Medication Guide before you start taking EPZICOM and each time you get
834 a refill. There may be new information. This information does not take the place of
835 talking to your healthcare provider about your medical condition or your treatment.
836 Be sure to carry your EPZICOM Warning Card with you at all times.

837

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

839 **1. Serious allergic reaction (hypersensitivity reaction).** EPZICOM contains
840 abacavir (also contained in ZIAGEN[®] and TRIZIVIR[®]). Patients taking EPZICOM
841 may have a serious allergic reaction (hypersensitivity reaction) that can cause
842 death. Your risk of this allergic reaction is much higher if you have a gene
843 variation called HLA-B*5701. Your healthcare provider can determine with a
844 blood test if you have this gene variation.

845 **If you get a symptom from 2 or more of the following groups while**
846 **taking EPZICOM, call your healthcare provider right away to find out if**
847 **you should stop taking EPZICOM.**
848

	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

849
850 A list of these symptoms is on the Warning Card your pharmacist gives you.
851 **Carry this Warning Card with you at all times.**

852 **If you stop EPZICOM because of an allergic reaction, never take**
853 **EPZICOM (abacavir sulfate and lamivudine) or any other**
854 **abacavir-containing medicine (ZIAGEN and TRIZIVIR) again.** If you take
855 EPZICOM or any other abacavir-containing medicine again after you have had an
856 allergic reaction, **within hours** you may get **life-threatening symptoms** that
857 may include **very low blood pressure** or **death**. If you stop EPZICOM for any
858 other reason, even for a few days, and you are not allergic to EPZICOM, talk
859 with your healthcare provider before taking it again. Taking EPZICOM again can
860 cause a serious allergic or life-threatening reaction, even if you never had an
861 allergic reaction to it before.

862 **If your healthcare provider tells you that you can take EPZICOM again,**
863 **start taking it when you are around medical help or people who can call**
864 **a healthcare provider if you need one.**

865 **2. Lactic Acidosis (buildup of acid in the blood).** Some human
866 **immunodeficiency virus (HIV) medicines, including EPZICOM, can cause**
867 **a rare but serious condition called lactic acidosis. Lactic acidosis is a**
868 **serious medical emergency that can cause death and must be treated in**
869 **the hospital.**

870 **Call your healthcare provider right away if you get any of the following**
871 **signs or symptoms of lactic acidosis:**

- 872 • you feel very weak or tired
- 873 • you have unusual (not normal) muscle pain

- 874 • you have trouble breathing
- 875 • you have stomach pain with nausea and vomiting
- 876 • you feel cold, especially in your arms and legs
- 877 • you feel dizzy or light-headed
- 878 • you have a fast or irregular heartbeat

879 **3. Serious liver problems. Some people who have taken medicines like**
880 **EPZICOM have developed serious liver problems called hepatotoxicity,**
881 **with liver enlargement (hepatomegaly) and fat in the liver (steatosis).**
882 **Hepatomegaly with steatosis is a serious medical emergency that can**
883 **cause death.**

884 **Call your healthcare provider right away if you get any of the following**
885 **signs or symptoms of liver problems:**

- 886 • your skin or the white part of your eyes turns yellow (jaundice)
- 887 • your urine turns dark
- 888 • your bowel movements (stools) turn light in color
- 889 • you don't feel like eating food for several days or longer
- 890 • you feel sick to your stomach (nausea)
- 891 • you have lower stomach area (abdominal) pain

892 **You may be more likely to get lactic acidosis or serious liver problems if**
893 **you are female, very overweight, or have been taking nucleoside**
894 **analogue medicines for a long time.**

895 **4. Use with interferon and ribavirin-based regimens.** Worsening of liver
896 disease (sometimes resulting in death) has occurred in patients infected with
897 both HIV and hepatitis C virus who are taking anti-HIV medicines and are also
898 being treated for hepatitis C with interferon with or without ribavirin. If you are
899 taking EPZICOM as well as interferon with or without ribavirin and you
900 experience side effects, be sure to tell your healthcare provider.

901 **5. If you have HIV and hepatitis B virus infection, your hepatitis B virus**
902 **infection may get worse if you stop taking EPZICOM.**

- 903 • Take EPZICOM exactly as prescribed.
- 904 • Do not run out of EPZICOM.
- 905 • Do not stop EPZICOM without talking to your healthcare provider.

906 Your healthcare provider should monitor your health and do regular blood tests to
907 check your liver if you stop taking EPZICOM.

908 **What is EPZICOM?**

909 EPZICOM is a prescription medicine used to treat HIV infection. EPZICOM contains
910 2 medicines: abacavir (ZIAGEN) and lamivudine or 3TC (EPIVIR®). Both of these

911 medicines are called nucleoside analogue reverse transcriptase inhibitors (NRTIs).
912 When used together, they help lower the amount of HIV in your blood.

- 913 • **EPZICOM does not cure HIV infection or AIDS.**
- 914 • It is not known if EPZICOM will help you live longer or have fewer of the medical
915 problems that people get with HIV or AIDS.
- 916 • It is very important that you see your healthcare provider regularly while you
917 are taking EPZICOM.
- 918 • It is not known if EPZICOM is safe or effective in children under the age of 18.

919 **Who should not take EPZICOM?**

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

- 921 • **are allergic to abacavir or any of the ingredients in EPZICOM. See the**
922 **end of this Medication Guide for a complete list of ingredients in**
923 **EPZICOM.**
- 924 • **have certain liver problems**

925 **What should I tell my healthcare provider before taking EPZICOM?**

926 **Before you take EPZICOM tell your healthcare provider if you:**

- 927 • **have been tested and know whether or not you have a particular gene**
928 **variation called HLA-B*5701**
- 929 • **have hepatitis B virus infection or have other liver problems**
- 930 • **have kidney problems**
- 931 • **have heart problems, smoke, or have diseases that increase your risk of**
932 **heart disease such as high blood pressure, high cholesterol, or diabetes.**
- 933 • **are pregnant or plan to become pregnant.** It is not known if EPZICOM will
934 harm your unborn baby. Talk to your healthcare provider if you are pregnant or
935 plan to become pregnant.

936 **Pregnancy Registry.** If you take EPZICOM while you are pregnant, talk to your
937 healthcare provider about how you can take part in the Pregnancy Registry for
938 EPZICOM. The purpose of the pregnancy registry is to collect information about
939 the health of you and your baby.

- 940 • **are breastfeeding or plan to breastfeed. Do not breastfeed.** Lamivudine is
941 excreted in human breast milk. We do not know if abacavir can be passed to
942 your baby in your breast milk and whether it could harm your baby. Also,
943 mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the
944 baby in the breast milk.

945 **Tell your healthcare provider about all the medicines you take**, including
946 prescription and nonprescription medicines, vitamins, and herbal supplements.

947 **Especially tell your healthcare provider if you take:**

- 948 • alcohol
- 949 • medicines used to treat hepatitis viruses such as interferon or ribavirin.
- 950 • methadone
- 951 • ATRIPLA[®] (efavirenz/emtricitabine/and tenofovir disoproxil fumarate)
- 952 • COMBIVIR[®] (lamivudine and zidovudine)
- 953 • COMPLERA[™] (emtricitabine/rilpivirine/tenofovir disoproxil fumarate)
- 954 • EMTRIVA[®] (emtricitabine)
- 955 • EPIVIR or EPIVIR-HBV[®] (lamivudine)
- 956 • TRIZIVIR (abacavir sulfate, lamivudine, and zidovudine)
- 957 • TRUVADA[®] (emtricitabine/tenofovir disoproxil fumarate)
- 958 • ZIAGEN (abacavir sulfate)

959 Ask your healthcare provider if you are not sure if you take one of the medicines
960 listed above.

961 EPZICOM may affect the way other medicines work, and other medicines may affect
962 how EPZICOM works.

963 Know the medicines you take. Keep a list of your medicines with you to show to
964 your healthcare provider and pharmacist when you get a new medicine.

965 **How should I take EPZICOM?**

- 966 • **Take EPZICOM exactly as your healthcare provider tells you to take it.**
- 967 • EPZICOM may be taken with or without food.
- 968 • Do not skip doses.
- 969 • **Do not let your EPZICOM run out.**

970 If you stop your anti-HIV medicines, even for a short time, the amount of virus in
971 your blood may increase and the virus may become harder to treat. If you take too
972 much EPZICOM, call your healthcare provider or poison control center or go to the
973 nearest hospital emergency room right away.

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

- 975 • **EPZICOM can cause serious side effects including allergic reactions,**
976 **lactic acidosis, and liver problems. See “What is the most important**
977 **information I should know about EPZICOM?”**

- 978 • **Changes in immune system (Immune Reconstitution Syndrome).** Your
979 immune system may get stronger and begin to fight infections that have been
980 hidden in your body for a long time. Tell your healthcare provider if you start
981 having new or worse symptoms of infection after you start taking EPZICOM.
- 982 • **Changes in body fat (fat redistribution).** Changes in body fat (lipoatrophy or
983 lipodystrophy) can happen in some people taking antiretroviral medicines
984 including EPZICOM.
- 985 • These changes may include:
 - 986 • more fat in or around your trunk, upper back and neck (buffalo hump),
987 breast, or chest
 - 988 • loss of fat in your legs, arms, or face
- 989 • **Heart attack (myocardial infarction).** Some HIV medicines including
990 EPZICOM may increase your risk of heart attack.

991 **The most common side effects of EPZICOM include:**

- 992 • trouble sleeping
- 993 • depression
- 994 • headache
- 995 • tiredness
- 996 • dizziness
- 997 • nausea
- 998 • diarrhea
- 999 • rash
- 1000 • fever

1001 Tell your healthcare provider if you have any side effect that bothers you or that
1002 does not go away.

1003 These are not all the possible side effects of EPZICOM. For more information, ask
1004 your healthcare provider or pharmacist.

1005 Call your doctor for medical advice about side effects. You may report side effects
1006 to FDA at 1-800-FDA-1088.

1007 **How should I store EPZICOM?**

1008 Store EPZICOM at 59°F to 86°F (15°C to 30°C).

1009 **Keep EPZICOM and all medicines out of the reach of children.**

1010 **General information for safe and effective use of EPZICOM.**

- 1011 Avoid doing things that can spread HIV-1 infection to others.
- 1012 • **Do not share needles or other injection equipment.**
 - 1013 • **Do not share personal items that can have blood or body fluids on them,**
 - 1014 **like toothbrushes and razor blades.**
 - 1015 • **Do not have any kind of sex without protection.** Always practice safe sex
 - 1016 by using a latex or polyurethane condom to lower the chance of sexual contact
 - 1017 with semen, vaginal secretions, or blood.

1018 Medicines are sometimes prescribed for purposes other than those listed in a
1019 Medication Guide. Do not use EPZICOM for a condition for which it was not
1020 prescribed. Do not give EPZICOM to other people, even if they have the same
1021 symptoms that you have. It may harm them.

1022 This Medication Guide summarizes the most important information about EPZICOM.
1023 If you would like more information, talk with your healthcare provider. You can ask
1024 your healthcare provider or pharmacist for the information about EPZICOM that is
1025 written for healthcare professionals.

1026 For more information go to www.EPZICOM.com or call 1-877-844-8872.

1027 **What are the ingredients in EPZICOM?**

1028 Active ingredients: abacavir sulfate and lamivudine

1029 Inactive ingredients: magnesium stearate, microcrystalline cellulose, sodium starch
1030 glycolate, and OPADRY® orange YS-1-13065-A, a film coating made of FD&C Yellow
1031 No. 6, hypromellose, polyethylene glycol 400, polysorbate 80, and titanium dioxide.
1032

1033 This Medication Guide has been approved by the US Food and Drug Administration.

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1039

1040

1041 Manufactured for:



1042 **ViiV**
1043 **Healthcare**

1044 Research Triangle Park, NC 27709

1045 by:



1046

1047 GlaxoSmithKline

1048 Research Triangle Park, NC 27709

1049 Lamivudine is manufactured under agreement from

1050 **Shire Pharmaceuticals Group plc**

1051 Basingstoke, UK

1052

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1055 March 2012

1056 EPZ:MG