

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)

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)

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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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 greater than 5%) in an adult HIV-1 clinical trial 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. (7.1)
- Methadone: An increased methadone dose may be required in a small number of patients. (7.3)

USE IN SPECIFIC POPULATIONS

- Lactation: Breastfeeding not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 02/2015

7 DRUG INTERACTIONS

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- 7.2 Interferon- and Ribavirin-based Regimens
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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**

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

7 **Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by a**
8 **sign or symptom in 2 or more of the following groups: (1) fever, (2) rash, (3)**
9 **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 hypersensitivity**
22 **cannot be ruled out, even when other diagnoses are possible.**

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

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

30 **Lactic Acidosis and Severe Hepatomegaly**

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

34 **Exacerbations of Hepatitis B**

35 **Severe acute exacerbations of hepatitis B have been reported in patients who are**
36 **co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and**
37 **have discontinued lamivudine, which is one component of EPZICOM. Hepatic function**
38 **should be monitored closely with both clinical and laboratory follow-up for at least several**
39 **months in patients who discontinue EPZICOM and are co-infected with HIV-1 and HBV.**
40 **If appropriate, initiation of anti-hepatitis B therapy may be warranted [see Warnings and**
41 **Precautions (5.3)].**

42 **1 INDICATIONS AND USAGE**

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

45 Additional important information on the use of EPZICOM for treatment of HIV-1 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 • EPZICOM can be taken with or without food.

57 **2.1 Adult Patients**

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

60 **2.2 Dosage Adjustment**

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

- 62 • patients requiring dosage adjustment such as those with creatinine clearance less than 50 mL
63 per min,
- 64 • patients with hepatic impairment.

65 Use of EPIVIR[®] (lamivudine) oral solution or tablets and ZIAGEN[®] (abacavir sulfate) oral
66 solution may be considered.

67 **3 DOSAGE FORMS AND STRENGTHS**

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

71 **4 CONTRAINDICATIONS**

72 EPZICOM tablets are contraindicated in patients with:

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

78 **5 WARNINGS AND PRECAUTIONS**

79 **5.1 Hypersensitivity Reaction**

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

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

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

95 **Signs and Symptoms of Hypersensitivity**

96 Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by a sign or
97 symptom in 2 or more of the following groups.

98 Group 1: Fever

99 Group 2: Rash

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

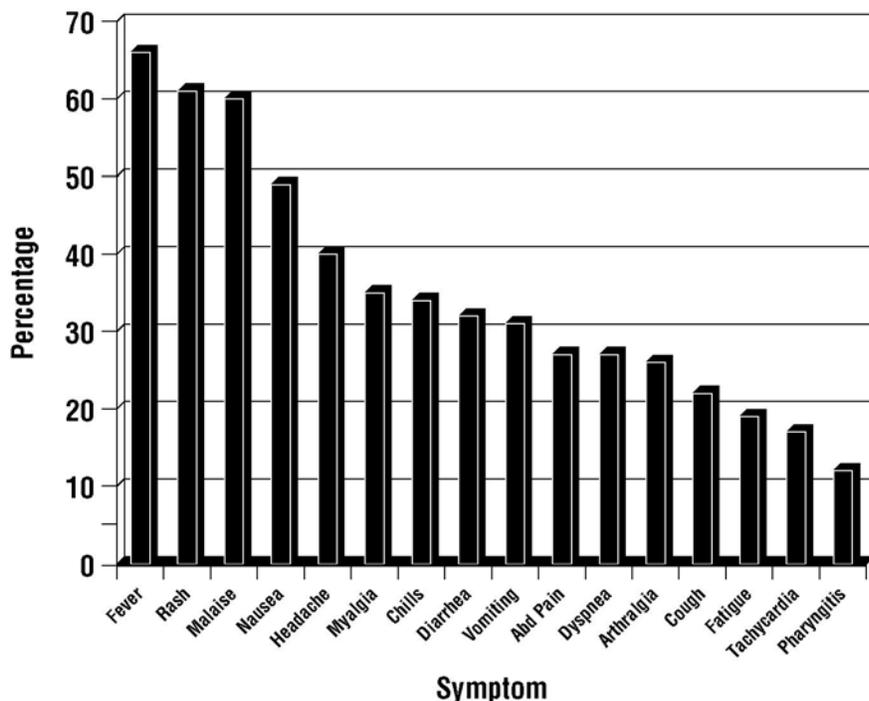
101 Group 4: Constitutional (including generalized malaise, fatigue, or achiness)

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

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

105 Hypersensitivity to abacavir was reported in approximately 8% of 2,670 subjects (n = 206) in
106 9 clinical trials (range: 2% to 9%) with enrollment from November 1999 to February 2002. Data
107 on time to onset and symptoms of suspected hypersensitivity were collected on a detailed data
108 collection module. The frequencies of symptoms are shown in Figure 1. Symptoms usually
109 appeared within the first 6 weeks of treatment with abacavir, although the reaction may occur at
110 any time during therapy. Median time to onset was 9 days; 89% appeared within the first
111 6 weeks; 95% of subjects reported symptoms from 2 or more of the 5 groups listed above.

112 **Figure 1: Hypersensitivity-related Symptoms Reported with Greater than or Equal to 10%**
113 **Frequency in Clinical Trials (n = 206 Subjects)**



114
115 Other less common signs and symptoms of hypersensitivity include lethargy, myolysis, edema,
116 abnormal chest x-ray findings (predominantly infiltrates, which can be localized), and
117 paresthesia. Anaphylaxis, liver failure, renal failure, hypotension, adult respiratory distress
118 syndrome, respiratory failure, and death have occurred in association with hypersensitivity
119 reactions. In one trial, 4 subjects (11%) receiving ZIAGEN 600 mg once daily experienced
120 hypotension with a hypersensitivity reaction compared with 0 subjects receiving ZIAGEN
121 300 mg twice daily.

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

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

130 Clinical Management of Hypersensitivity

131 Discontinue EPZICOM as soon as a hypersensitivity reaction is suspected. To minimize the risk
132 of a life-threatening hypersensitivity reaction, permanently discontinue EPZICOM if
133 hypersensitivity cannot be ruled out, even when other diagnoses are possible (e.g., acute onset
134 respiratory diseases such as pneumonia, bronchitis, pharyngitis, or influenza; gastroenteritis; or
135 reactions to other medications).

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

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

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

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

155 Risk Factor

156 *HLA-B*5701 Allele:* Trials have shown that carriage of the HLA-B*5701 allele is associated
157 with a significantly increased risk of a hypersensitivity reaction to abacavir.

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

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

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

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

179 **5.2 Lactic Acidosis and Severe Hepatomegaly with Steatosis**

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

189 **5.3 Patients with HIV-1 and Hepatitis B Virus Co-infection**

190 Posttreatment Exacerbations of Hepatitis

191 In clinical trials in non-HIV-1-infected subjects treated with lamivudine for chronic HBV,
192 clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation
193 of lamivudine. These exacerbations have been detected primarily by serum ALT elevations in
194 addition to re-emergence of HBV DNA. Although most events appear to have been self-limited,

195 fatalities have been reported in some cases. Similar events have been reported from
196 post-marketing experience after changes from lamivudine-containing HIV-1 treatment regimens
197 to non-lamivudine-containing regimens in patients infected with both HIV-1 and HBV. The
198 causal relationship to discontinuation of lamivudine treatment is unknown. Patients should be
199 closely monitored with both clinical and laboratory follow-up for at least several months after
200 stopping treatment. There is insufficient evidence to determine whether re-initiation of
201 lamivudine alters the course of posttreatment exacerbations of hepatitis.

202 Emergence of Lamivudine-resistant HBV

203 Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B
204 in subjects dually infected with HIV-1 and HBV. In non-HIV-1-infected subjects treated with
205 lamivudine for chronic hepatitis B, emergence of lamivudine-resistant HBV has been detected
206 and has been associated with diminished treatment response (see full prescribing information for
207 EPIVIR-HBV® [lamivudine] tablets and oral solution for additional information). Emergence of
208 hepatitis B virus variants associated with resistance to lamivudine has also been reported in
209 HIV-1-infected subjects who have received lamivudine-containing antiretroviral regimens in the
210 presence of concurrent infection with hepatitis B virus.

211 **5.4 Use with Interferon- and Ribavirin-based Regimens**

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

225 **5.5 Immune Reconstitution Syndrome**

226 Immune reconstitution syndrome has been reported in patients treated with combination
227 antiretroviral therapy, including EPZICOM. During the initial phase of combination
228 antiretroviral treatment, patients whose immune systems respond may develop an inflammatory
229 response to indolent or residual opportunistic infections (such as *Mycobacterium avium*
230 infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which
231 may necessitate further evaluation and treatment.

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

235 **5.6 Fat Redistribution**

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

241 **5.7 Myocardial Infarction**

242 In a published prospective, observational, epidemiological trial designed to investigate the rate of
243 myocardial infarction in patients on combination antiretroviral therapy, the use of abacavir
244 within the previous 6 months was correlated with an increased risk of myocardial infarction
245 (MI).¹ In a sponsor-conducted pooled analysis of clinical trials, no excess risk of MI was
246 observed in abacavir-treated subjects as compared with control subjects. In totality, the available
247 data from the observational cohort and from clinical trials are inconclusive.

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

251 **5.8 Use with Other Abacavir-, Lamivudine-, and/or Emtricitabine-containing** 252 **Products**

253 EPZICOM contains fixed doses of 2 nucleoside analogues, abacavir and lamivudine, and should
254 not be administered concomitantly with other abacavir-containing and/or lamivudine-containing
255 products, including ZIAGEN (abacavir sulfate) tablets and oral solution, EPIVIR (lamivudine)
256 tablets and oral solution, EPIVIR-HBV (lamivudine) tablets and oral solution, COMBIVIR[®]
257 (lamivudine and zidovudine) tablets, or TRIZIVIR[®] (abacavir sulfate, lamivudine, and
258 zidovudine) tablets; or emtricitabine-containing products, including ATRIPLA[®]
259 (efavirenz/emtricitabine/tenofovir disoproxil fumarate) tablets, EMTRIVA[®] (emtricitabine)
260 capsules and oral solution, TRUVADA[®] (emtricitabine/tenofovir disoproxil fumarate) tablets, or
261 COMPLERA[®] (emtricitabine/rilpivirine/tenofovir disoproxil fumarate) tablets.

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

264 **6 ADVERSE REACTIONS**

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

- 266 • Serious and sometimes fatal hypersensitivity reaction. In one trial, once-daily dosing of
267 abacavir was associated with more severe hypersensitivity reactions [*see Boxed Warning,*
268 *Warnings and Precautions (5.1)*].
- 269 • Lactic acidosis and severe hepatomegaly [*see Boxed Warning, Warnings and Precautions*
270 *(5.2)*].
- 271 • Acute exacerbations of hepatitis B [*see Boxed Warning, Warnings and Precautions (5.3)*].
- 272 • Hepatic decompensation in patients co-infected with HIV-1 and Hepatitis C [*see Warnings*
273 *and Precautions (5.4)*].
- 274 • Immune reconstitution syndrome [*see Warnings and Precautions (5.5)*].
- 275 • Fat redistribution [*see Warnings and Precautions (5.6)*].
- 276 • Myocardial infarction [*see Warnings and Precautions (5.7)*].

277 **6.1 Clinical Trials Experience**

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

281 Therapy-naive Adults

282 Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe)
283 with a at least 5% frequency during therapy with ZIAGEN 600 mg once daily or ZIAGEN
284 300 mg twice daily, both in combination with lamivudine 300 mg once daily and efavirenz
285 600 mg once daily, are listed in Table 1.

286 **Table 1. Treatment-emergent (All Causality) Adverse Reactions of at Least Moderate**
 287 **Intensity (Grades 2-4, Greater than or Equal to 5% Frequency) in Therapy-naive Adults**
 288 **(CNA30021) through 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%

289 ^a Subjects receiving ZIAGEN 600 mg once daily, experienced a significantly higher incidence of
 290 severe drug hypersensitivity reactions and severe diarrhea compared with subjects who
 291 received ZIAGEN 300 mg twice daily. Five percent (5%) of subjects receiving ZIAGEN
 292 600 mg once daily had severe drug hypersensitivity reactions compared with 2% of subjects
 293 receiving ZIAGEN 300 mg twice daily. Two percent (2%) of subjects receiving ZIAGEN
 294 600 mg once daily had severe diarrhea while none of the subjects receiving ZIAGEN 300 mg
 295 twice daily had this event.

296 ^b CNA30024 was a multi-center, double-blind, controlled trial in which 649 HIV-1-infected,
 297 therapy-naive adults were randomized and received either ZIAGEN (300 mg twice daily),
 298 EPIVIR (150 mg twice daily), and efavirenz (600 mg once daily); or zidovudine (300 mg twice
 299 daily), EPIVIR (150 mg twice daily), and efavirenz (600 mg once daily). CNA30024 used
 300 double-blind ascertainment of suspected hypersensitivity reactions. During the blinded portion
 301 of the trial, suspected hypersensitivity to abacavir was reported by investigators in 9% of
 302 324 subjects in the abacavir group and 3% of 325 subjects in the zidovudine group.

303 **Laboratory Abnormalities**

304 Laboratory abnormalities observed in clinical trials of ZIAGEN were anemia, neutropenia, liver
 305 function test abnormalities, and elevations of CPK, blood glucose, and triglycerides. Additional
 306 laboratory abnormalities observed in clinical trials of EPIVIR were thrombocytopenia and
 307 elevated levels of bilirubin, amylase, and lipase.

308 The frequencies of treatment-emergent laboratory abnormalities were comparable between
309 treatment groups in CNA30021.

310 Other Adverse Events

311 In addition to adverse reactions listed above, other adverse events observed in the expanded
312 access program for abacavir were pancreatitis and increased GGT.

313 **6.2 Postmarketing Experience**

314 The following adverse reactions have been identified during post-approval use of abacavir,
315 lamivudine, and/or EPZICOM. Because these reactions are reported voluntarily from a
316 population of unknown size, it is not always possible to reliably estimate their frequency or
317 establish a causal relationship to drug exposures. These reactions have been chosen for inclusion
318 due to a combination of their seriousness, frequency of reporting, or potential causal connection
319 to abacavir, lamivudine, and/or EPZICOM.

320 Abacavir

321 *Cardiovascular:* Myocardial infarction.

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

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

329 Abacavir and Lamivudine

330 *Body as a Whole:* Redistribution/accumulation of body fat [*see Warnings and Precautions*
331 (5.6)].

332 *Digestive:* Stomatitis.

333 *Endocrine and Metabolic:* Hyperglycemia.

334 *General:* Weakness.

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

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

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

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

341 *Nervous*: Paresthesia, peripheral neuropathy, seizures.
342 *Respiratory*: Abnormal breath sounds/wheezing.
343 *Skin*: Alopecia, erythema multiforme, Stevens-Johnson syndrome.

344 **7 DRUG INTERACTIONS**

345 No drug interaction trials have been conducted using EPZICOM tablets [*see Clinical*
346 *Pharmacology (12.3)*].

347 **7.1 Ethanol**

348 Abacavir

349 Abacavir has no effect on the pharmacokinetic properties of ethanol. Ethanol decreases the
350 elimination of abacavir causing an increase in overall exposure [*see Clinical Pharmacology*
351 *(12.3)*].

352 **7.2 Interferon- and Ribavirin-based Regimens**

353 Lamivudine

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

360 **7.3 Methadone**

361 Abacavir

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

368 **7.4 Trimethoprim/Sulfamethoxazole (TMP/SMX)**

369 Lamivudine

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

373 **8 USE IN SPECIFIC POPULATIONS**

374 **8.1 Pregnancy**

375 Pregnancy Exposure Registry

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

379 Risk Summary

380 Available data from the Antiretroviral Pregnancy Registry show no difference in the risk of
381 overall major birth defects for abacavir or lamivudine compared with the background rate for
382 major birth defects of 2.7% in the US reference population of the Metropolitan Atlanta
383 Congenital Defects Program (MACDP). Abacavir produced fetal malformations and other
384 embryonic and fetal toxicities in rats at 35 times the human exposure at the recommended
385 clinical dose. Lamivudine produced embryonic toxicity in rabbits at a dose that produced similar
386 human exposures to the recommended clinical dose. The relevance of animal findings to human
387 pregnancy registry data is not known.

388 Data

389 *Human Data: Abacavir:* Based on prospective reports from the Antiretroviral Pregnancy
390 Registry of over 2,000 exposures to abacavir during pregnancy resulting in live births (including
391 over 900 exposed in the first trimester), there was no difference between abacavir and overall
392 birth defects compared with the background birth defect rate of 2.7% in the US reference
393 population of the MACDP. The prevalence of defects in the first trimester was 3.0% (95% CI:
394 2.0% to 4.4%).

395 *Lamivudine:* Based on prospective reports from the Antiretroviral Pregnancy Registry of
396 over 11,000 exposures to lamivudine during pregnancy resulting in live births (including over
397 4,300 exposed in the first trimester), there was no difference between lamivudine and overall
398 birth defects compared with the background birth defect rate of 2.7% in the U.S. reference
399 population of the MACDP. The prevalence of defects in the first trimester was 3.1% (95% CI:
400 2.6% to 3.7%).

401 Lamivudine pharmacokinetics were studied in pregnant women during 2 clinical trials conducted
402 in South Africa. The trials assessed pharmacokinetics in 16 women at 36 weeks gestation using
403 150 mg lamivudine twice daily with zidovudine, 10 women at 38 weeks gestation using 150 mg
404 lamivudine twice daily with zidovudine, and 10 women at 38 weeks gestation using lamivudine
405 300 mg twice daily without other antiretrovirals. These trials were not designed or powered to
406 provide efficacy information. Lamivudine pharmacokinetics in pregnant women were similar to
407 those seen in non-pregnant adults and in postpartum women. Lamivudine concentrations were
408 generally similar in maternal, neonatal, and umbilical cord serum samples. In a subset of
409 subjects, amniotic fluid specimens were collected following natural rupture of membranes and

410 confirmed that lamivudine crosses the placenta in humans. Amniotic fluid concentrations of
411 lamivudine were typically 2 times greater than maternal serum levels and ranged from 1.2 to
412 2.5 mcg per mL (150 mg twice daily) and 2.1 to 5.2 mcg per mL (300 mg twice daily).

413 *Animal Data: Abacavir:* Studies in pregnant rats showed that abacavir is transferred to the fetus
414 through the placenta. Fetal malformations (increased incidences of fetal anasarca and skeletal
415 malformations) and developmental toxicity (depressed fetal body weight and reduced
416 crown-rump length) were observed in rats at a dose which produced 35 times the human
417 exposure, based on AUC. Embryonic and fetal toxicities (increased resorptions, decreased fetal
418 body weights) and toxicities to the offspring (increased incidence of stillbirth and lower body
419 weights) occurred at half of the above-mentioned dose in separate fertility studies conducted in
420 rats. In the rabbit, no developmental toxicity and no increases in fetal malformations occurred at
421 doses that produced 8.5 times the human exposure at the recommended dose based on AUC.

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

429 **8.2 Lactation**

430 The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the
431 United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1
432 infection.

433 Because of the potential for HIV-1 transmission mothers should be instructed not to breastfeed.

434 **8.4 Pediatric Use**

435 Safety and effectiveness of EPZICOM in pediatric patients have not been established. EPZICOM
436 is not recommended for use in patients younger than 18 years because it cannot be dose adjusted.

437 **8.5 Geriatric Use**

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

443 **8.6 Patients with Impaired Renal Function**

444 EPZICOM is not recommended for patients with impaired renal function (creatinine clearance
445 less than 50 mL per min) because EPZICOM is a fixed-dose combination and the dosage of the
446 individual components cannot be adjusted.

447 **8.7 Patients with Impaired Hepatic Function**

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

450 **10 OVERDOSAGE**

451 If overdose occurs, the patient should be monitored, and standard supportive treatment applied as
452 required.

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

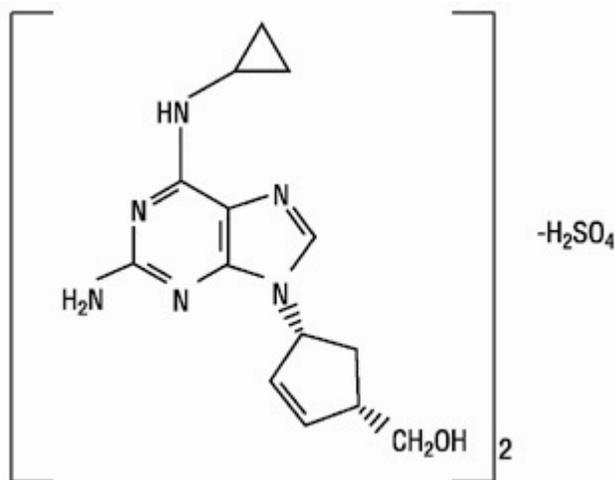
455 **Lamivudine:** One case of an adult ingesting 6 grams of lamivudine was reported; there were no
456 clinical signs or symptoms noted and hematologic tests remained normal. Because a negligible
457 amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal
458 dialysis,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

460 **11 DESCRIPTION**

461 **EPZICOM:** EPZICOM tablets contain the following 2 synthetic nucleoside analogues: abacavir
462 sulfate (ZIAGEN, also a component of TRIZIVIR) and lamivudine (also known as EPIVIR or
463 3TC) with inhibitory activity against HIV-1.

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

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

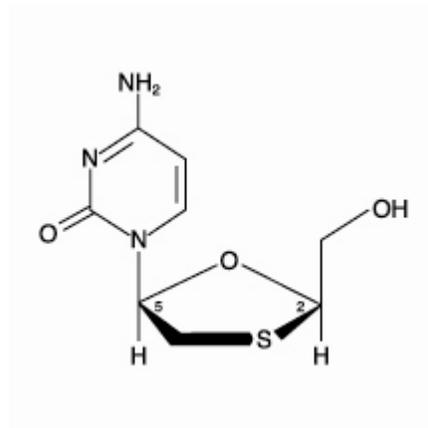


474

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

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

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



484

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

487 12 CLINICAL PHARMACOLOGY

488 12.1 Mechanism of Action

489 EPZICOM is an antiviral agent [see Microbiology (12.4)].

490 **12.3 Pharmacokinetics**

491 Pharmacokinetics in Adults

492 *EPZICOM*: In a single-dose, 3-way crossover bioavailability trial of 1 EPZICOM tablet versus
493 2 ZIAGEN tablets (2 x 300 mg) and 2 EPIVIR tablets (2 x 150 mg) administered simultaneously
494 in healthy subjects (n = 25), there was no difference in the extent of absorption, as measured by
495 the area under the plasma concentration-time curve (AUC) and maximal peak concentration
496 (C_{\max}), of each component.

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

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

513 The steady-state pharmacokinetic properties of the EPIVIR 300-mg tablet once daily for 7 days
514 compared with the EPIVIR 150-mg tablet twice daily for 7 days were assessed in a crossover
515 trial in 60 healthy subjects. EPIVIR 300 mg once daily resulted in lamivudine exposures that
516 were similar to EPIVIR 150 mg twice daily with respect to plasma $AUC_{24,ss}$; however, $C_{\max,ss}$
517 was 66% higher and the trough value was 53% lower compared with the 150-mg twice-daily
518 regimen. Intracellular lamivudine triphosphate exposures in peripheral blood mononuclear cells
519 were also similar with respect to $AUC_{24,ss}$ and $C_{\max 24,ss}$; however, trough values were lower
520 compared with the 150-mg twice-daily regimen. Inter-subject variability was greater for
521 intracellular lamivudine triphosphate concentrations versus lamivudine plasma trough
522 concentrations. The clinical significance of observed differences for both plasma lamivudine
523 concentrations and intracellular lamivudine triphosphate concentrations is not known.

524 In humans, abacavir and lamivudine are not significantly metabolized by cytochrome P450
525 enzymes.

526 The pharmacokinetic properties of abacavir and lamivudine in fasting subjects are summarized in
527 Table 2.

528 **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/h/kg)	0.80 ± 0.24	n = 6	0.33 ± 0.06	n = 20
Renal clearance (L/h/kg)	0.007 ± 0.008	n = 6	0.22 ± 0.06	n = 20
Elimination half-life (h)	1.45 ± 0.32	n = 20	5 to 7 ^b	

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

530 ^b Approximate range.

531 Effect of Food on Absorption of EPZICOM

532 EPZICOM may be administered with or without food. Administration with a high-fat meal in a
533 single-dose bioavailability trial resulted in no change in AUC_{last}, AUC_∞, and C_{max} for
534 lamivudine. Food did not alter the extent of systemic exposure to abacavir (AUC_∞), but the rate
535 of absorption (C_{max}) was decreased approximately 24% compared with fasted conditions
536 (n = 25). These results are similar to those from previous trials of the effect of food on abacavir
537 and lamivudine tablets administered separately.

538 Special Populations

539 *Renal Impairment: EPZICOM:* Because lamivudine requires dose adjustment in the presence
540 of renal insufficiency, EPZICOM is not recommended for use in patients with creatinine
541 clearance less than 50 mL per min [see *Dosage and Administration (2.2)*].

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

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

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

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

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

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

556 *Race: Abacavir*: There are no significant differences between blacks and whites in abacavir
557 pharmacokinetics.

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

559 Drug Interactions

560 The drug interactions described are based on trials conducted with the individual nucleoside
561 analogues. In humans, abacavir and lamivudine are not significantly metabolized by cytochrome
562 P450 enzymes nor do they inhibit or induce this enzyme system; therefore, it is unlikely that
563 clinically significant drug interactions will occur with drugs metabolized through these
564 pathways.

565 *Abacavir: Lamivudine and Zidovudine*: Fifteen HIV-1-infected subjects were enrolled in a
566 crossover-designed drug interaction trial evaluating single doses of abacavir (600 mg),
567 lamivudine (150 mg), and zidovudine (300 mg) alone or in combination. Analysis showed no
568 clinically relevant changes in the pharmacokinetics of abacavir with the addition of lamivudine
569 or zidovudine or the combination of lamivudine and zidovudine. Lamivudine exposure (AUC
570 decreased 15%) and zidovudine exposure (AUC increased 10%) did not show clinically relevant
571 changes with concurrent abacavir.

572 *Methadone*: In a trial of 11 HIV-1-infected subjects receiving methadone-maintenance
573 therapy (40 mg and 90 mg daily), with 600 mg of ZIAGEN twice daily (twice the currently
574 recommended dose), oral methadone clearance increased 22% (90% CI: 6% to 42%) [*see Drug*
575 *Interactions (7.3)*].

576 *Lamivudine: Zidovudine*: No clinically significant alterations in lamivudine or zidovudine
577 pharmacokinetics were observed in 12 asymptomatic HIV-1-infected adult subjects given a
578 single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg
579 every 12 h).

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

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

587 **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 every 8 h 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%	↔

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

590 **12.4 Microbiology**591 **Mechanism of Action**

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

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

605 **Antiviral Activity**

606 *Abacavir*: The antiviral activity of abacavir against HIV-1 was evaluated against a T-cell tropic
607 laboratory strain HIV-1_{IIIB} in lymphoblastic cell lines, a monocyte/macrophage tropic laboratory
608 strain HIV-1_{BaL} in primary monocytes/macrophages, and clinical isolates in peripheral blood
609 mononuclear cells. The concentration of drug necessary to effect viral replication by 50 percent
610 (EC₅₀) ranged from 3.7 to 5.8 μM (1 μM = 0.28 mcg per mL) and 0.07 to 1.0 μM against
611 HIV-1_{IIIB} and HIV-1_{BaL}, respectively, and was 0.26 ± 0.18 μM against 8 clinical isolates. The
612 EC₅₀ values of abacavir against different HIV-1 clades (A-G) ranged from 0.0015 to 1.05 μM,
613 and against HIV-2 isolates, from 0.024 to 0.49 μM. Ribavirin (50 μM) had no effect on the anti-
614 HIV-1 activity of abacavir in cell culture.

615 *Lamivudine*: The antiviral activity of lamivudine against HIV-1 was assessed in a number of
616 cell lines (including monocytes and fresh human peripheral blood lymphocytes) using standard
617 susceptibility assays. EC₅₀ values were in the range of 0.003 to 15 μM (1 μM = 0.23 mcg per
618 mL). HIV-1 from therapy-naive subjects with no amino acid substitutions associated with
619 resistance gave median EC₅₀ values of 0.429 μM (range: 0.200 to 2.007 μM) from Virco (n = 92
620 baseline samples from COLA40263) and 2.35 μM (range: 1.37 to 3.68 μM) from Monogram
621 Biosciences (n = 135 baseline samples from ESS30009). The EC₅₀ values of lamivudine against
622 different HIV-1 clades (A-G) ranged from 0.001 to 0.120 μM, and against HIV-2 isolates from
623 0.003 to 0.120 μM in peripheral blood mononuclear cells. Ribavirin (50 μM) decreased the anti-
624 HIV-1 activity of lamivudine by 3.5 fold in MT-4 cells.

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

634 Resistance

635 HIV-1 isolates with reduced susceptibility to the combination of abacavir and lamivudine have
636 been selected in cell culture and have also been obtained from subjects failing
637 abacavir/lamivudine-containing regimens. Genotypic characterization of
638 abacavir/lamivudine-resistant viruses selected in cell culture identified amino acid substitutions
639 M184V/I, K65R, L74V, and Y115F in HIV-1 RT.

640 Genotypic analysis of isolates selected in cell culture and recovered from abacavir-treated
641 subjects demonstrated that amino acid substitutions K65R, L74V, Y115F, and M184V/I in
642 HIV-1 RT contributed to abacavir resistance. Genotypic analysis of isolates selected in cell
643 culture and recovered from lamivudine-treated subjects showed that the resistance was due to a

644 specific amino acid substitution in HIV-1 RT at codon 184 changing the methionine to either
645 isoleucine or valine (M184V/I). In a trial of therapy-naive adults receiving ZIAGEN 600 mg
646 once daily (n = 384) or 300 mg twice daily (n = 386) in a background regimen of lamivudine
647 300 mg and efavirenz 600 mg once daily (CNA30021), the incidence of virologic failure at
648 48 weeks was similar between the 2 groups (11% in both arms). Genotypic (n = 38) and
649 phenotypic analyses (n = 35) of virologic failure isolates from this trial showed that the RT
650 substitutions that emerged during abacavir/lamivudine once-daily and twice-daily therapy were
651 K65R, L74V, Y115F, and M184V/I. The abacavir- and lamivudine-associated resistance
652 substitution M184V/I was the most commonly observed substitution in virologic failure isolates
653 from subjects receiving abacavir/lamivudine once daily (56%, 10 of 18) and twice daily (40%, 8
654 of 20).

655 Thirty-nine percent (7 of 18) of the isolates from subjects who experienced virologic failure in
656 the abacavir once-daily arm had a greater than 2.5-fold decrease in abacavir susceptibility with a
657 median-fold decrease of 1.3 (range: 0.5 to 11) compared with 29% (5 of 17) of the failure
658 isolates in the twice-daily arm with a median-fold decrease of 0.92 (range: 0.7 to 13). Fifty-six
659 percent (10 of 18) of the virologic failure isolates in the once-daily abacavir group compared
660 with 41% (7 of 17) of the failure isolates in the twice-daily abacavir group had a greater than
661 2.5-fold decrease in lamivudine susceptibility with median-fold changes of 81 (range: 0.79 to
662 greater than 116) and 1.1 (range: 0.68 to greater than 116) in the once-daily and twice-daily
663 abacavir arms, respectively.

664 Cross-resistance

665 Cross-resistance has been observed among NRTIs. Viruses containing abacavir and lamivudine
666 resistance-associated amino acid substitutions, namely, K65R, L74V, M184V, and Y115F,
667 exhibit cross-resistance to didanosine, emtricitabine, lamivudine, tenofovir, and zalcitabine in
668 cell culture and in subjects. The K65R substitution can confer resistance to abacavir, didanosine,
669 emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine; the L74V substitution can confer
670 resistance to abacavir, didanosine, and zalcitabine; and the M184V substitution can confer
671 resistance to abacavir, didanosine, emtricitabine, lamivudine, and zalcitabine.

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

677 **13 NONCLINICAL TOXICOLOGY**

678 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

679 Carcinogenicity

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

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

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

691 Mutagenicity

692 *Abacavir*: Abacavir induced chromosomal aberrations both in the presence and absence of
693 metabolic activation in an in vitro cytogenetic study in human lymphocytes. Abacavir was
694 mutagenic in the absence of metabolic activation, although it was not mutagenic in the presence
695 of metabolic activation in an L5178Y mouse lymphoma assay. Abacavir was clastogenic in
696 males and not clastogenic in females in an in vivo mouse bone marrow micronucleus assay.
697 Abacavir was not mutagenic in bacterial mutagenicity assays in the presence and absence of
698 metabolic activation.

699 *Lamivudine*: Lamivudine was mutagenic in an L5178Y mouse lymphoma assay and clastogenic
700 in a cytogenetic assay using cultured human lymphocytes. Lamivudine was not mutagenic in a
701 microbial mutagenicity assay, in an in vitro cell transformation assay, in a rat micronucleus test,
702 in a rat bone marrow cytogenetic assay, and in an assay for unscheduled DNA synthesis in rat
703 liver.

704 Impairment of Fertility

705 Abacavir or lamivudine induced no adverse effects on the mating performance or fertility of
706 male and female rats at doses producing systemic exposure levels approximately 8 or 130 times,
707 respectively, higher than those in humans at the recommended dose based on body surface area
708 comparisons.

709 **13.2 Animal Toxicology and/or Pharmacology**

710 Myocardial degeneration was found in mice and rats following administration of abacavir for
711 2 years. The systemic exposures were equivalent to 7 to 24 times the expected systemic exposure
712 in humans. The clinical relevance of this finding has not been determined.

713 **14 CLINICAL STUDIES**

714 EPZICOM

715 There have been no clinical trials conducted with EPZICOM. One EPZICOM tablet given once
 716 daily is an alternative regimen to EPIVIR tablets 300 mg once daily plus ZIAGEN tablets
 717 2 x 300 mg once daily as a component of antiretroviral therapy.

718 The following trial was conducted with the individual components of EPZICOM.

719 Therapy-naive Adults

720 CNA30021 was an international, multi-center, double-blind, controlled trial in which
 721 770 HIV-1-infected, therapy-naive adults were randomized and received either ZIAGEN 600 mg
 722 once daily or ZIAGEN 300 mg twice daily, both in combination with EPIVIR 300 mg once daily
 723 and efavirenz 600 mg once daily. The double-blind treatment duration was at least 48 weeks.
 724 Trial participants had a mean age of 37 years; were male (81%), white (54%), black (27%), and
 725 American Hispanic (15%). The median baseline CD4+ cell count was 262 cells per mm³ (range:
 726 21 to 918 cells per mm³) and the median baseline plasma HIV-1 RNA was 4.89 log₁₀ copies per
 727 mL (range: 2.60 to 6.99 log₁₀ copies per mL).

728 The outcomes of randomized treatment are provided in Table 4.

729 **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%

730 ^a Subjects achieved and maintained confirmed HIV-1 RNA less than 50 copies per mL (less than
 731 400 copies per mL) through Week 48 (Roche AMPLICOR Ultrasensitive HIV-1 MONITOR[®]
 732 standard test version 1.0).

733 ^b Includes viral rebound, failure to achieve confirmed less than 50 copies per mL (less than
 734 400 copies per mL) by Week 48, and insufficient viral load response.

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

737 After 48 weeks of therapy, the median CD4+ cell count increases from baseline were 188 cells
 738 per mm³ in the group receiving ZIAGEN 600 mg once daily and 200 cells per mm³ in the group
 739 receiving ZIAGEN 300 mg twice daily. Through Week 48, 6 subjects (2%) in the group
 740 receiving ZIAGEN 600 mg once daily (4 CDC classification C events and 2 deaths) and
 741 10 subjects (3%) in the group receiving ZIAGEN 300 mg twice daily (7 CDC classification C
 742 events and 3 deaths) experienced clinical disease progression. None of the deaths were attributed
 743 to trial medications.

744 **15 REFERENCES**

- 745 1. Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study Group. *Lancet*.
746 2008;371 (9622):1417-1426.

747 **16 HOW SUPPLIED/STORAGE AND HANDLING**

748 EPZICOM is available as tablets. Each tablet contains 600 mg of abacavir as abacavir sulfate and
749 300 mg of lamivudine. The tablets are orange, film-coated, modified capsule-shaped, and
750 debossed with GS FC2 on one side with no markings on the reverse side. They are packaged as
751 follows:

752 Bottles of 30 tablets (NDC 49702-206-13).

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

755 **17 PATIENT COUNSELING INFORMATION**

756 Advise the patient to read the FDA-approved patient labeling (Medication Guide).

757 Hypersensitivity Reaction

758 Inform patients:

- 759 • that a Medication Guide and Warning Card summarizing the symptoms of the abacavir
760 hypersensitivity reaction and other product information will be dispensed by the pharmacist
761 with each new prescription and refill of EPZICOM, and instruct the patient to read the
762 Medication Guide and Warning Card every time to obtain any new information that may be
763 present about EPZICOM. The complete text of the Medication Guide is reprinted at the end
764 of this document.
- 765 • to carry the Warning Card with them.
- 766 • how to identify a hypersensitivity reaction [*see Warnings and Precautions (5.1), Medication*
767 *Guide*].
- 768 • that if they develop symptoms consistent with a hypersensitivity reaction they should call
769 their healthcare provider right away to determine if they should stop taking EPZICOM.
- 770 • that a hypersensitivity reaction can worsen and lead to hospitalization or death if EPZICOM
771 is not immediately discontinued.
- 772 • that in one trial, more severe hypersensitivity reactions were seen when ZIAGEN was dosed
773 600 mg once daily.
- 774 • to not restart EPZICOM or any other abacavir-containing product following a
775 hypersensitivity reaction because more severe symptoms can occur within hours and may
776 include life-threatening hypotension and death.

- 777 • that a hypersensitivity reaction is usually reversible if it is detected promptly and EPZICOM
778 is stopped right away.
- 779 • that if they have interrupted EPZICOM for reasons other than symptoms of hypersensitivity
780 (for example, those who have an interruption in drug supply), a serious or fatal
781 hypersensitivity reaction may occur with reintroduction of abacavir.
- 782 • to not restart EPZICOM or any other abacavir-containing product without medical
783 consultation and that restarting abacavir needs to be undertaken only if medical care can be
784 readily accessed by the patient or others.
- 785 • EPZICOM should not be administered concomitantly with ATRIPLA, COMBIVIR,
786 COMPLERA, EMTRIVA, EPIVIR, EPIVIR-HBV, TRIZIVIR, TRUVADA, or ZIAGEN.

787 Lactic Acidosis/Hepatomegaly

788 Inform patients that some HIV medicines, including EPZICOM, can cause a rare, but serious
789 condition called lactic acidosis with liver enlargement (hepatomegaly) [*see Boxed Warning,*
790 *Warnings and Precautions (5.2)*].

791 HIV-1/ HBV Co-infection

792 Inform patients co-infected with HIV-1 and HBV that deterioration of liver disease has occurred
793 in some cases when treatment with lamivudine was discontinued. Advise patients to discuss any
794 changes in regimen with their physician [*see Warnings and Precautions (5.3)*].

795 HIV-1/HCV Co-infection

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

799 Redistribution/Accumulation of Body Fat

800 Inform patients that redistribution or accumulation of body fat may occur in patients receiving
801 antiretroviral therapy and that the cause and long-term health effects of these conditions are not
802 known at this time [*see Warnings and Precautions (5.6)*].

803 Information About HIV-1 Infection

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

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

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

819

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828

829 Manufactured for



830

831 ViiV Healthcare

832 Research Triangle Park, NC 27709

833 by:



834
835 GlaxoSmithKline
836 Research Triangle Park, NC 27709

837
838 Lamivudine is manufactured under agreement from
839 **Shire Pharmaceuticals Group plc**
840 Basingstoke, UK

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842 EPZ:XPI

843

844

845 **MEDICATION GUIDE**

846 **EPZICOM® (ep' zih com)**

847 (abacavir sulfate and lamivudine)

848 **tablets**

849

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

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

855 **1. Serious allergic reaction (hypersensitivity reaction).** EPZICOM contains
856 abacavir (also contained in ZIAGEN® and TRIZIVIR®). Patients taking EPZICOM
857 may have a serious allergic reaction (hypersensitivity reaction) that can cause
858 death. Your risk of this allergic reaction is much higher if you have a gene
859 variation called HLA-B*5701. Your healthcare provider can determine with a
860 blood test if you have this gene variation.

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

	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

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

866 **If you stop EPZICOM because of an allergic reaction, never take**
867 **EPZICOM (abacavir sulfate and lamivudine) or any other**
868 **abacavir-containing medicine (ZIAGEN and TRIZIVIR) again.** If you take
869 EPZICOM or any other abacavir-containing medicine again after you have had an
870 allergic reaction, **within hours** you may get **life-threatening symptoms** that
871 may include **very low blood pressure** or **death**. If you stop EPZICOM for any
872 other reason, even for a few days, and you are not allergic to EPZICOM, talk
873 with your healthcare provider before taking it again. Taking EPZICOM again can
874 cause a serious allergic or life-threatening reaction, even if you never had an
875 allergic reaction to it before.

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

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

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

- 886 • you feel very weak or tired
- 887 • you have unusual (not normal) muscle pain
- 888 • you have trouble breathing
- 889 • you have stomach pain with nausea and vomiting

- 890 • you feel cold, especially in your arms and legs
- 891 • you feel dizzy or light-headed
- 892 • you have a fast or irregular heartbeat

893 **3. Serious liver problems. Some people who have taken medicines like**
894 **EPZICOM have developed serious liver problems called hepatotoxicity,**
895 **with liver enlargement (hepatomegaly) and fat in the liver (steatosis).**
896 **Hepatomegaly with steatosis is a serious medical emergency that can**
897 **cause death.**

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

- 900 • your skin or the white part of your eyes turns yellow (jaundice)
- 901 • your urine turns dark
- 902 • your bowel movements (stools) turn light in color
- 903 • you don't feel like eating food for several days or longer
- 904 • you feel sick to your stomach (nausea)
- 905 • you have lower stomach area (abdominal) pain

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

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

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

- 917 • Take EPZICOM exactly as prescribed.
- 918 • Do not run out of EPZICOM.
- 919 • Do not stop EPZICOM without talking to your healthcare provider.

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

922 **What is EPZICOM?**

923 EPZICOM is a prescription medicine used to treat HIV infection. EPZICOM contains
924 2 medicines: abacavir (ZIAGEN) and lamivudine or 3TC (EPIVIR®). Both of these
925 medicines are called nucleoside analogue reverse transcriptase inhibitors (NRTIs).
926 When used together, they help lower the amount of HIV in your blood.

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

933 **Who should not take EPZICOM?**

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

- 935 • **are allergic to abacavir or any of the ingredients in EPZICOM. See the**
936 **end of this Medication Guide for a complete list of ingredients in**
937 **EPZICOM.**
- 938 • **have certain liver problems.**

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

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

- 941 • **have been tested and know whether or not you have a particular gene**
942 **variation called HLA-B*5701.**
- 943 • **have hepatitis B virus infection or have other liver problems.**
- 944 • **have kidney problems.**
- 945 • **have heart problems, smoke, or have diseases that increase your risk of**
946 **heart disease such as high blood pressure, high cholesterol, or diabetes.**
- 947 • **are pregnant or plan to become pregnant.** Taking EPZICOM during
948 pregnancy has not been associated with an increased risk of birth defects. Talk
949 to your healthcare provider if you are pregnant or plan to become pregnant.

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

- 954 • are breastfeeding or plan to breastfeed. **Do not breastfeed if you take**
955 **EPZICOM.**

956 • You should not breastfeed if you have HIV-1 because of the risk of passing
957 HIV-1 to your baby.

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

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

- 961 • alcohol
- 962 • medicines used to treat hepatitis viruses such as interferon or ribavirin.
- 963 • methadone
- 964 • ATRIPLA[®] (efavirenz/emtricitabine/tenofovir disoproxil fumarate)
- 965 • COMBIVIR[®] (lamivudine and zidovudine)
- 966 • COMPLERA[®] (emtricitabine/rilpivirine/tenofovir disoproxil fumarate)
- 967 • EMTRIVA[®] (emtricitabine)
- 968 • EPIVIR or EPIVIR-HBV[®] (lamivudine)
- 969 • TRIZIVIR (abacavir sulfate, lamivudine, and zidovudine)
- 970 • TRUVADA[®] (emtricitabine/tenofovir disoproxil fumarate)
- 971 • ZIAGEN (abacavir sulfate)

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

974 EPZICOM may affect the way other medicines work, and other medicines may affect
975 how EPZICOM works.

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

978 **How should I take EPZICOM?**

- 979 • **Take EPZICOM exactly as your healthcare provider tells you to take it.**
- 980 • EPZICOM may be taken with or without food.
- 981 • Do not skip doses.
- 982 • **Do not let your EPZICOM run out.**

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

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

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

991 • **Changes in immune system (Immune Reconstitution Syndrome).** Your
992 immune system may get stronger and begin to fight infections that have been
993 hidden in your body for a long time. Tell your healthcare provider if you start
994 having new or worse symptoms of infection after you start taking EPZICOM.

995 • **Changes in body fat (fat redistribution).** Changes in body fat (lipoatrophy or
996 lipodystrophy) can happen in some people taking antiretroviral medicines
997 including EPZICOM.

998 These changes may include:

999 • more fat in or around your trunk, upper back and neck (buffalo hump),
1000 breast, or chest

1001 • loss of fat in your legs, arms, or face

1002 • **Heart attack (myocardial infarction).** Some HIV medicines including
1003 EPZICOM may increase your risk of heart attack.

1004 **The most common side effects of EPZICOM include:**

1005 • trouble sleeping

1006 • depression

1007 • headache

1008 • tiredness

1009 • dizziness

1010 • nausea

1011 • diarrhea

1012 • rash

1013 • fever

1014 Tell your healthcare provider if you have any side effect that bothers you or that
1015 does not go away.

1016 These are not all the possible side effects of EPZICOM. For more information, ask
1017 your healthcare provider or pharmacist.

1018 Call your doctor for medical advice about side effects. You may report side effects
1019 to FDA at 1-800-FDA-1088.

1020 **How should I store EPZICOM?**

1021 Store EPZICOM at 59°F to 86°F (15°C to 30°C).

1022 **Keep EPZICOM and all medicines out of the reach of children.**

1023 **General information for safe and effective use of EPZICOM.**

1024 Avoid doing things that can spread HIV infection to others.

1025 • **Do not re-use or share needles or other injection equipment.**

1026 • **Do not share personal items that can have blood or body fluids on them,**
1027 **like toothbrushes and razor blades.**

1028 • **Do not have any kind of sex without protection.** Always practice safer sex
1029 by using a latex or polyurethane condom to lower the chance of sexual contact
1030 with any body fluids such as semen, vaginal secretions, or blood.

1031 Medicines are sometimes prescribed for purposes other than those listed in a
1032 Medication Guide. Do not use EPZICOM for a condition for which it was not
1033 prescribed. Do not give EPZICOM to other people, even if they have the same
1034 symptoms that you have. It may harm them.

1035 This Medication Guide summarizes the most important information about EPZICOM.
1036 If you would like more information, talk with your healthcare provider. You can ask
1037 your healthcare provider or pharmacist for the information about EPZICOM that is
1038 written for healthcare professionals.

1039 For more information go to www.EPZICOM.com or call 1-877-844-8872.

1040 **What are the ingredients in EPZICOM?**

1041 Active ingredients: abacavir sulfate and lamivudine

1042 Inactive ingredients: magnesium stearate, microcrystalline cellulose, sodium starch
1043 glycolate, and OPADRY® orange YS-1-13065-A, a film coating made of FD&C Yellow
1044 No. 6, hypromellose, polyethylene glycol 400, polysorbate 80, and titanium dioxide.

1045

1046 This Medication Guide has been approved by the US Food and Drug Administration.

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1053 products.

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1056 Manufactured for:



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1058 ViiV Healthcare

1059 Research Triangle Park, NC 27709

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1061 by:



1062

1063 GlaxoSmithKline

1064 Research Triangle Park, NC 27709

1065 Lamivudine is manufactured under agreement from

1066 **Shire Pharmaceuticals Group plc**

1067 Basingstoke, UK

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1069 February 2015

1070 EPZ: XMG