

## 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  
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)

### DOSAGE FORMS AND STRENGTHS

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

## FULL PRESCRIBING INFORMATION: CONTENTS\*

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

#### 1 INDICATIONS AND USAGE

#### 2 DOSAGE AND ADMINISTRATION

- 2.1 Adult Patients
- 2.2 Dosage Adjustment

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

- 5.1 Hypersensitivity Reaction
- 5.2 Lactic Acidosis and Severe Hepatomegaly With Steatosis
- 5.3 Patients With HIV-1 and Hepatitis B Virus Co-Infection
- 5.4 Use With Interferon- and Ribavirin-Based Regimens
- 5.5 Immune Reconstitution Syndrome
- 5.6 Fat Redistribution
- 5.7 Myocardial Infarction
- 5.8 Use With Other Abacavir-, Lamivudine- and/or Emtricitabine-Containing Products

#### 6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

### 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](http://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)

### USE IN SPECIFIC POPULATIONS

Pregnancy: Physicians are encouraged to register patients in the Antiretroviral Pregnancy Registry by calling 1-800-258-4263. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE.

Revised: February 2011

## 7 DRUG INTERACTIONS

- 7.1 Ethanol
- 7.2 Interferon- and Ribavirin-Based Regimens
- 7.3 Methadone
- 7.4 Trimethoprim/Sulfamethoxazole (TMP/SMX)

## 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Patients With Impaired Renal Function
- 8.7 Patients With Impaired Hepatic Function

## 10 OVERDOSAGE

## 11 DESCRIPTION

## 12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics
- 12.4 Microbiology

## 13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

## 14 CLINICAL STUDIES

## 15 REFERENCES

## 16 HOW SUPPLIED/STORAGE AND HANDLING

## 17 PATIENT COUNSELING INFORMATION

\*Sections or subsections omitted from the full prescribing information are not listed.

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<sup>®</sup> (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<sup>®</sup> (lamivudine) Oral Solution or Tablets and ZIAGEN<sup>®</sup> (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)

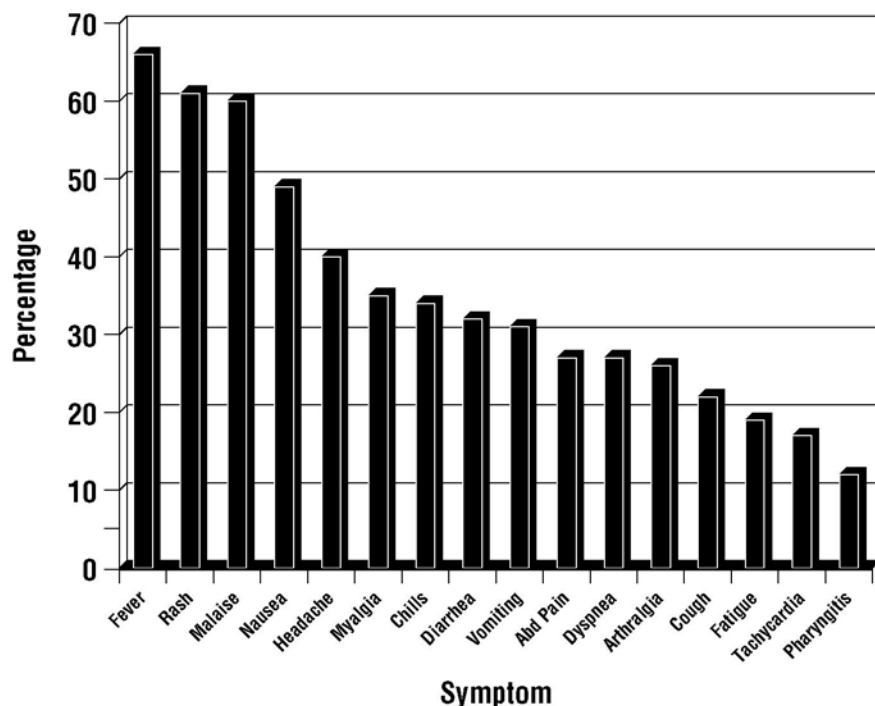
105 Hypersensitivity to abacavir following the presentation of a single sign or symptom has  
106 been reported infrequently.

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.

115

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



118

119

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.

127

128

129

130

131

132

133

134

135

136

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<sup>®</sup> [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 **5.6 Fat Redistribution**

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

244 **5.7 Myocardial Infarction**

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

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

254 **5.8 Use With Other Abacavir-, Lamivudine-, and/or Emtricitabine-Containing**  
255 **Products**



256 EPZICOM contains fixed doses of 2 nucleoside analogues, abacavir and lamivudine, and  
257 should not be administered concomitantly with other abacavir-containing and/or  
258 lamivudine-containing products (ZIAGEN, EPIVIR, COMBIVIR<sup>®</sup> [lamivudine and zidovudine]  
259 Tablets, or TRIZIVIR<sup>®</sup> [abacavir sulfate, lamivudine, and zidovudine] Tablets); or  
260 emtricitabine-containing products, including ATRIPLA<sup>®</sup> (efavirenz, emtricitabine, and tenofovir  
261 disoproxil fumarate) Tablets, EMTRIVA<sup>®</sup> (emtricitabine) Capsules and Oral Solution, or  
262 TRUVADA<sup>®</sup> (emtricitabine and tenofovir disoproxil fumarate) Tablets.

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

## 265 **6 ADVERSE REACTIONS**

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

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

### 279 **6.1 Clinical Trials Experience**

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

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

287

288 **Table 1. Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate**  
 289 **Intensity (Grades 2-4, ≥5% Frequency) in Therapy-Naive Adults (CNA30021) Through**  
 290 **48 Weeks of Treatment**

Adverse Event	ZIAGEN 600 mg q.d. plus EPIVIR plus Efavirenz (n = 384)	ZIAGEN 300 mg b.i.d. plus EPIVIR plus Efavirenz (n = 386)
<b>Drug hypersensitivity<sup>a,b</sup></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 <sup>a</sup>	5%	6%
Rash	5%	5%
Pyrexia	5%	3%
Abdominal pain/gastritis	4%	5%
Abnormal dreams	4%	5%
Anxiety	3%	5%

291 <sup>a</sup> Subjects receiving ZIAGEN 600 mg once daily, experienced a significantly higher incidence  
 292 of severe drug hypersensitivity reactions and severe diarrhea compared with subjects who  
 293 received ZIAGEN 300 mg twice daily. Five percent (5%) of subjects receiving ZIAGEN  
 294 600 mg once daily had severe drug hypersensitivity reactions compared with 2% of subjects  
 295 receiving ZIAGEN 300 mg twice daily. Two percent (2%) of subjects receiving ZIAGEN  
 296 600 mg once daily had severe diarrhea while none of the subjects receiving ZIAGEN 300 mg  
 297 twice daily had this event.

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

306  
 307 Laboratory Abnormalities: Laboratory abnormalities observed in clinical studies of  
 308 ZIAGEN were anemia, neutropenia, liver function test abnormalities, and elevations of CPK,  
 309 blood glucose, and triglycerides. Additional laboratory abnormalities observed in clinical studies  
 310 of EPIVIR were thrombocytopenia and elevated levels of bilirubin, amylase, and lipase.

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

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

## 316 **6.2 Postmarketing Experience**

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

### 323 Abacavir:

324 *Cardiovascular:* Myocardial infarction.

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

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

### 332 Abacavir and Lamivudine:

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

335 *Digestive:* Stomatitis.

336 *Endocrine and Metabolic:* Hyperglycemia.

337 *General:* Weakness.

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

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

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

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

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

345 *Respiratory:* Abnormal breath sounds/wheezing.

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

## 347 **7 DRUG INTERACTIONS**

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

350 **7.1 Ethanol**

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

354 **7.2 Interferon- and Ribavirin-Based Regimens**

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

361 **7.3 Methadone**

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

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

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

372 **8 USE IN SPECIFIC POPULATIONS**

373 **8.1 Pregnancy**

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

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

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

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

394 Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant  
395 women exposed to EPZICOM or other antiretroviral agents, an Antiretroviral Pregnancy  
396 Registry has been established. Physicians are encouraged to register patients by calling 1-800-  
397 258-4263.

### 398 **8.3 Nursing Mothers**

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

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

402 Lamivudine: Lamivudine is excreted in human breast milk and into the milk of lactating  
403 rats.

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

### 407 **8.4 Pediatric Use**

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

### 411 **8.5 Geriatric Use**

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

### 417 **8.6 Patients With Impaired Renal Function**

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

### 421 **8.7 Patients With Impaired Hepatic Function**

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

## 424 **10 OVERDOSAGE**

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

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

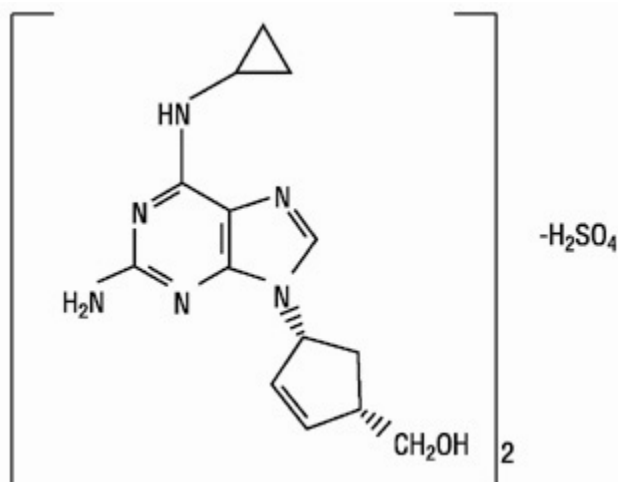
## 430 11 DESCRIPTION

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

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

439 **Abacavir Sulfate:** The chemical name of abacavir sulfate is (1*S*,*cis*)-4-[2-amino-6-  
440 (cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1). Abacavir  
441 sulfate is the enantiomer with 1*S*, 4*R* absolute configuration on the cyclopentene ring. It has a  
442 molecular formula of (C<sub>14</sub>H<sub>18</sub>N<sub>6</sub>O)<sub>2</sub>•H<sub>2</sub>SO<sub>4</sub> and a molecular weight of 670.76 daltons. It has the  
443 following structural formula:

444



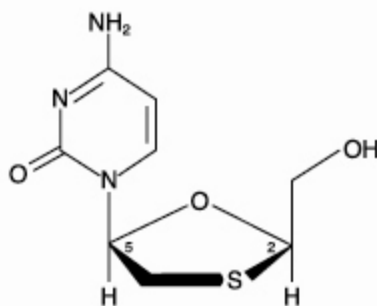
445

446

447 Abacavir sulfate is a white to off-white solid with a solubility of approximately  
448 77 mg/mL in distilled water at 25°C.

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

451 **Lamivudine:** The chemical name of lamivudine is (2*R*,*cis*)-4-amino-1-(2-  
452 hydroxymethyl-1,3-oxathiolan-5-yl)-(1*H*)-pyrimidin-2-one. Lamivudine is the (-)enantiomer of a  
453 dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2',3'-dideoxy, 3'-  
454 thiacytidine. It has a molecular formula of C<sub>8</sub>H<sub>11</sub>N<sub>3</sub>O<sub>3</sub>S and a molecular weight of 229.3 daltons.  
455 It has the following structural formula:



456  
457 Lamivudine is a white to off-white crystalline solid with a solubility of approximately  
458 70 mg/mL in water at 20°C.

## 459 12 CLINICAL PHARMACOLOGY

### 460 12.1 Mechanism of Action

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

### 462 12.3 Pharmacokinetics

463 Pharmacokinetics in Adults: EPZICOM: In a single-dose, 3-way crossover  
464 bioavailability study of 1 EPZICOM Tablet versus 2 ZIAGEN Tablets (2 x 300 mg) and  
465 2 EPIVIR Tablets (2 x 150 mg) administered simultaneously in healthy subjects (n = 25), there  
466 was no difference in the extent of absorption, as measured by the area under the plasma  
467 concentration-time curve (AUC) and maximal peak concentration ( $C_{max}$ ), of each component.

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

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

484 The steady-state pharmacokinetic properties of the EPIVIR 300-mg tablet once daily for  
485 7 days compared with the EPIVIR 150-mg tablet twice daily for 7 days were assessed in a

486 crossover study in 60 healthy volunteers. EPIVIR 300 mg once daily resulted in lamivudine  
 487 exposures that were similar to EPIVIR 150 mg twice daily with respect to plasma AUC<sub>24,ss</sub>;  
 488 however, C<sub>max,ss</sub> was 66% higher and the trough value was 53% lower compared with the  
 489 150-mg twice-daily regimen. Intracellular lamivudine triphosphate exposures in peripheral blood  
 490 mononuclear cells were also similar with respect to AUC<sub>24,ss</sub> and C<sub>max24,ss</sub>; however, trough  
 491 values were lower compared with the 150-mg twice-daily regimen. Inter-subject variability was  
 492 greater for intracellular lamivudine triphosphate concentrations versus lamivudine plasma trough  
 493 concentrations. The clinical significance of observed differences for both plasma lamivudine  
 494 concentrations and intracellular lamivudine triphosphate concentrations is not known.

495 In humans, abacavir and lamivudine are not significantly metabolized by cytochrome  
 496 P450 enzymes.

497 The pharmacokinetic properties of abacavir and lamivudine in fasting subjects are  
 498 summarized in Table 2.

499

500

**Table 2. Pharmacokinetic Parameters<sup>a</sup> for Abacavir and Lamivudine in Adults**

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

501 <sup>a</sup> Data presented as mean ± standard deviation except where noted.

502 <sup>b</sup> Approximate range.

503

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

547 *Abacavir: Lamivudine and Zidovudine:* Fifteen HIV-1-infected subjects were  
548 enrolled in a crossover-designed drug interaction study evaluating single doses of abacavir  
549 (600 mg), lamivudine (150 mg), and zidovudine (300 mg) alone or in combination. Analysis  
550 showed no clinically relevant changes in the pharmacokinetics of abacavir with the addition of  
551 lamivudine or zidovudine or the combination of lamivudine and zidovudine. Lamivudine  
552 exposure (AUC decreased 15%) and zidovudine exposure (AUC increased 10%) did not show  
553 clinically relevant changes with concurrent abacavir.

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

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

560 given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine  
 561 (300 mg q 12 hr).

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

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

571 **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%	↔

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

574

## 575 12.4 Microbiology

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

581 incorporated nucleotide analogue prevents the formation of the 5' to 3' phosphodiester linkage  
582 essential for DNA chain elongation, and therefore, the viral DNA growth is terminated. CBV-TP  
583 is a weak inhibitor of cellular DNA polymerases  $\alpha$ ,  $\beta$ , and  $\gamma$ .

584 **Lamivudine:** Lamivudine is a synthetic nucleoside analogue. Intracellularly  
585 lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate  
586 (3TC-TP). The principal mode of action of 3TC-TP is inhibition of RT via DNA chain  
587 termination after incorporation of the nucleotide analogue. CBV-TP and 3TC-TP are weak  
588 inhibitors of cellular DNA polymerases  $\alpha$ ,  $\beta$ , and  $\gamma$ .

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

598 **Lamivudine:** The antiviral activity of lamivudine against HIV-1 was assessed in a  
599 number of cell lines (including monocytes and fresh human peripheral blood lymphocytes) using  
600 standard susceptibility assays.  $EC_{50}$  values were in the range of 0.003 to 15  $\mu\text{M}$   
601 (1  $\mu\text{M}$  = 0.23 mcg/mL). HIV-1 from therapy-naive subjects with no amino acid substitutions  
602 associated with resistance gave median  $EC_{50}$  values of 0.429  $\mu\text{M}$  (range: 0.200 to 2.007  $\mu\text{M}$ )  
603 from Virco (n = 92 baseline samples from COLA40263) and 2.35  $\mu\text{M}$  (1.37 to 3.68  $\mu\text{M}$ ) from  
604 Monogram Biosciences (n = 135 baseline samples from ESS30009). The  $EC_{50}$  values of  
605 lamivudine against different HIV-1 clades (A-G) ranged from 0.001 to 0.120  $\mu\text{M}$ , and against  
606 HIV-2 isolates from 0.003 to 0.120  $\mu\text{M}$  in peripheral blood mononuclear cells. Ribavirin  
607 (50  $\mu\text{M}$ ) decreased the anti-HIV-1 activity of lamivudine by 3.5 fold in MT-4 cells.

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

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

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

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

637 Thirty-nine percent (7/18) of the isolates from subjects who experienced virologic failure  
638 in the abacavir once-daily arm had a >2.5-fold decrease in abacavir susceptibility with a  
639 median-fold decrease of 1.3 (range: 0.5 to 11) compared with 29% (5/17) of the failure isolates  
640 in the twice-daily arm with a median-fold decrease of 0.92 (range: 0.7 to 13). Fifty-six percent  
641 (10/18) of the virologic failure isolates in the once-daily abacavir group compared with 41%  
642 (7/17) of the failure isolates in the twice-daily abacavir group had a >2.5-fold decrease in  
643 lamivudine susceptibility with median-fold changes of 81 (range: 0.79 to >116) and 1.1 (range:  
644 0.68 to >116) in the once-daily and twice-daily abacavir arms, respectively.

645 **Cross-Resistance:** Cross-resistance has been observed among NRTIs. Viruses  
646 containing abacavir and lamivudine resistance-associated amino acid substitutions, namely,  
647 K65R, L74V, M184V, and Y115F, exhibit cross-resistance to didanosine, emtricitabine,  
648 lamivudine, tenofovir, and zalcitabine in cell culture and in subjects. The K65R substitution can  
649 confer resistance to abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and  
650 zalcitabine; the L74V substitution can confer resistance to abacavir, didanosine, and zalcitabine;  
651 and the M184V substitution can confer resistance to abacavir, didanosine, emtricitabine,  
652 lamivudine, and zalcitabine.

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

658 **13 NONCLINICAL TOXICOLOGY**

659 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

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

672 Mutagenicity: Abacavir: Abacavir induced chromosomal aberrations both in the  
673 presence and absence of metabolic activation in an in vitro cytogenetic study in human  
674 lymphocytes. Abacavir was mutagenic in the absence of metabolic activation, although it was  
675 not mutagenic in the presence of metabolic activation in an L5178Y mouse lymphoma assay.  
676 Abacavir was clastogenic in males and not clastogenic in females in an in vivo mouse bone  
677 marrow micronucleus assay. Abacavir was not mutagenic in bacterial mutagenicity assays in the  
678 presence and absence of metabolic activation.

679 Lamivudine: Lamivudine was mutagenic in an L5178Y mouse lymphoma assay and  
680 clastogenic in a cytogenetic assay using cultured human lymphocytes. Lamivudine was not  
681 mutagenic in a microbial mutagenicity assay, in an in vitro cell transformation assay, in a rat  
682 micronucleus test, in a rat bone marrow cytogenetic assay, and in an assay for unscheduled DNA  
683 synthesis in rat liver.

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

688 **13.2 Animal Toxicology and/or Pharmacology**

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

692 **14 CLINICAL STUDIES**

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

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

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

705 The outcomes of randomized treatment are provided in Table 4.  
 706

707 **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 <sup>a</sup>	64% (71%)	65% (72%)
Virologic failure <sup>b</sup>	11% (5%)	11% (5%)
Discontinued due to adverse reactions	13%	11%
Discontinued due to other reasons <sup>c</sup>	11%	13%

708 <sup>a</sup> Subjects achieved and maintained confirmed HIV-1 RNA <50 copies/mL (<400 copies/mL)  
 709 through Week 48 (Roche AMPLICOR Ultrasensitive HIV-1 MONITOR<sup>®</sup> standard test  
 710 version 1.0).

711 <sup>b</sup> Includes viral rebound, failure to achieve confirmed <50 copies/mL (<400 copies/mL) by  
 712 Week 48, and insufficient viral load response.

713 <sup>c</sup> Includes consent withdrawn, lost to follow-up, protocol violations, clinical progression, and  
 714 other.

715  
 716 After 48 weeks of therapy, the median CD4+ cell count increases from baseline were  
 717 188 cells/mm<sup>3</sup> in the group receiving ZIAGEN 600 mg once daily and 200 cells/mm<sup>3</sup> in the  
 718 group receiving ZIAGEN 300 mg twice daily. Through Week 48, 6 subjects (2%) in the group  
 719 receiving ZIAGEN 600 mg once daily (4 CDC classification C events and 2 deaths) and  
 720 10 subjects (3%) in the group receiving ZIAGEN 300 mg twice daily (7 CDC classification C  
 721 events and 3 deaths) experienced clinical disease progression. None of the deaths were attributed  
 722 to study medications.

723 **15 REFERENCES**

- 724 1. Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study Group. *Lancet*.  
 725 2008;371 (9622):1417-1426.

726 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

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

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

734 **17 PATIENT COUNSELING INFORMATION**

735 See Medication Guide.

736 Hypersensitivity Reaction: Inform patients:

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

765 Lactic Acidosis/Hepatomegaly: Inform patients that some HIV medicines, including  
766 EPZICOM, can cause a rare, but serious condition called lactic acidosis with liver enlargement  
767 (hepatomegaly).

768 Co-infection With HIV-1 and HBV: Patients co-infected with HIV-1 and HBV should  
769 be informed that deterioration of liver disease has occurred in some cases when treatment with  
770 lamivudine was discontinued. Patients should be advised to discuss any changes in regimen with  
771 their physician [*see Warnings and Precautions (5.2)*].

772 Redistribution/Accumulation of Body Fat: Inform patients that redistribution or  
773 accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause  
774 and long-term health effects of these conditions are not known at this time.

775 Information About HIV-1 Infection: EPZICOM is not a cure for HIV-1 infection and  
776 patients may continue to experience illnesses associated with HIV-1 infection, including  
777 opportunistic infections. Patients should remain under the care of a physician when using  
778 EPZICOM. Advise patients that the use of EPZICOM has not been shown to reduce the risk of  
779 transmission of HIV-1 to others through sexual contact or blood contamination. Patients should  
780 be informed to take all HIV medications exactly as prescribed.

781 Importance of Taking EPZICOM as Prescribed: Inform patients to take EPZICOM  
782 on a regular dosing schedule and to avoid missing doses. EPZICOM Tablets are for oral  
783 ingestion only.

784  
785 COMBIVIR, EPIVIR, EPZICOM, TRIZIVIR, and ZIAGEN are registered trademarks of ViiV  
786 Healthcare.

787  
788 The other brands listed are trademarks of their respective owners and are not trademarks of ViiV  
789 Healthcare. The makers of these brands are not affiliated with and do not endorse ViiV  
790 Healthcare or its products.

791  
792 Manufactured for:



793  
794 ViiV Healthcare  
795 Research Triangle Park, NC 27709

796  
797 by:





798  
799 GlaxoSmithKline  
800 Research Triangle Park, NC 27709  
801  
802 Lamivudine is manufactured under agreement from  
803 **Shire Pharmaceuticals Group plc**  
804 Basingstoke, UK  
805

806 ©2011, ViiV Healthcare. All rights reserved.

807  
808 February 2011  
809 EPZ:4PI

810

## 811 **MEDICATION GUIDE**

### 812 **EPZICOM® (ep' zih com)**

813 (abacavir sulfate and lamivudine)

#### 814 **Tablets**

815

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

820

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

822 **1. Serious allergic reaction (hypersensitivity reaction).** EPZICOM contains  
823 abacavir (also contained in ZIAGEN® and TRIZIVIR®). Patients taking EPZICOM  
824 may have a serious allergic reaction (hypersensitivity reaction) that can cause  
825 death. Your risk of this allergic reaction is much higher if you have a gene  
826 variation called HLA-B\*5701. Your healthcare provider can determine with a  
827 blood test if you have this gene variation.

828 **If you get a symptom from 2 or more of the following groups while**  
829 **taking EPZICOM, call your healthcare provider right away to find out**  
830 **if 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

832

833

834

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

835

836

837

838

839

840

841

842

843

844

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

845

846

847

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

848

849

850

851

852

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

853

854

855

856

857

858

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

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

- 859 • you feel cold, especially in your arms and legs
- 860 • you feel dizzy or light-headed
- 861 • you have a fast or irregular heartbeat

862 **3. Serious liver problems. Some people who have taken medicines like**  
863 **EPZICOM have developed serious liver problems called hepatotoxicity,**  
864 **with liver enlargement (hepatomegaly) and fat in the liver (steatosis).**  
865 **Hepatomegaly with steatosis is a serious medical emergency that can**  
866 **cause death.**

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

- 869 • your skin or the white part of your eyes turns yellow (jaundice)
- 870 • your urine turns dark
- 871 • your bowel movements (stools) turn light in color
- 872 • you don't feel like eating food for several days or longer
- 873 • you feel sick to your stomach (nausea)
- 874 • you have lower stomach area (abdominal) pain

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

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

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

- 886 • Take EPZICOM exactly as prescribed.
- 887 • Do not run out of EPZICOM.
- 888 • Do not stop EPZICOM without talking to your healthcare provider.
- 889 • Your healthcare provider should monitor your health and do regular blood  
890 tests to check your liver if you stop taking EPZICOM.

### 891 **What is EPZICOM?**

892 EPZICOM is a prescription medicine used to treat HIV infection. EPZICOM contains  
893 2 medicines: abacavir (ZIAGEN) and lamivudine or 3TC (EPIVIR®). Both of these  
894 medicines are called nucleoside analogue reverse transcriptase inhibitors (NRTIs).  
895 When used together, they help lower the amount of HIV in your blood.

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

902 **Who should not take EPZICOM?**

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

- 904 • **are allergic to abacavir or any of the ingredients in EPZICOM. See the**
- 905 **end of this Medication Guide for a complete list of ingredients in**
- 906 **EPZICOM.**
- 907 • **have certain liver problems**

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

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

- 910 • **have been tested and know whether or not you have a particular gene**
- 911 **variation called HLA-B\*5701**
- 912 • **have hepatitis B virus infection or have other liver problems**
- 913 • **have kidney problems**
- 914 • **have heart problems, smoke, or have diseases that increase your risk of**
- 915 **heart disease such as high blood pressure, high cholesterol, or diabetes.**
- 916 • **are pregnant or plan to become pregnant.** It is not known if EPZICOM will
- 917 harm your unborn baby. Talk to your healthcare provider if you are pregnant or
- 918 plan to become pregnant.

919 **Pregnancy Registry.** If you take EPZICOM while you are pregnant, talk to your

920 healthcare provider about how you can take part in the Pregnancy Registry for

921 EPZICOM. The purpose of the pregnancy registry is to collect information about

922 the health of you and your baby.

- 923 • **are breastfeeding or plan to breastfeed.** EPZICOM can pass into your breast
- 924 milk. You should not breastfeed if you are taking EPZICOM. If you are a woman
- 925 who has or will have a baby while taking EPZICOM, talk to your healthcare
- 926 provider about the best way to feed your baby. The Center for Disease Control
- 927 and Prevention (CDC) recommend that HIV-infected mothers **not** breastfeed to
- 928 avoid the risk of passing HIV infection to your baby.

929 **Tell your healthcare provider about all the medicines you take,** including

930 prescription and nonprescription medicines, vitamins, and herbal supplements.

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

- 932 • alcohol
- 933 • medicines used to treat hepatitis viruses such as interferon or ribavirin.
- 934 • methadone
- 935 • ATRIPLA<sup>®</sup> (efavirenz, emtricitabine, and tenofovir)
- 936 • COMBIVIR<sup>®</sup> (lamivudine and zidovudine)
- 937 • EMTRIVA<sup>®</sup> (emtricitabine)
- 938 • EPIVIR or EPIVIR-HBV<sup>®</sup> (lamivudine, 3TC)
- 939 • TRIZIVIR (abacavir sulfate, lamivudine, and zidovudine)
- 940 • TRUVADA<sup>®</sup> (emtricitabine and tenofovir)
- 941 • ZIAGEN (abacavir sulfate)

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

944 EPZICOM may affect the way other medicines work, and other medicines may affect  
945 how EPZICOM works.

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

948 **How should I take EPZICOM?**

- 949 • **Take EPZICOM exactly as your healthcare provider tells you to take it.**
- 950 • EPZICOM may be taken with or without food.
- 951 • Do not skip doses.
- 952 • **Do not let your EPZICOM run out.**

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

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

- 958 • **EPZICOM can cause serious side effects including allergic reactions,**  
959 **lactic acidosis, and liver problems. See “What is the most important**  
960 **information I should know about EPZICOM?”**
- 961 • **Changes in immune system (Immune Reconstitution Syndrome).** Your  
962 immune system may get stronger and begin to fight infections that have been  
963 hidden in your body for a long time. Tell your healthcare provider if you start  
964 having new or worse symptoms of infection after you start taking EPZICOM.

965 • **Changes in body fat (fat redistribution).** Changes in body fat (lipoatrophy or  
966 lipodystrophy) can happen in some people taking antiretroviral medicines  
967 including EPZICOM.

968 These changes may include:

- 969 ○ more fat in or around your trunk, upper back and neck (buffalo hump),
- 970 breast, or chest
- 971 ○ loss of fat in your legs, arms, or face

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

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

- 975 • trouble sleeping
- 976 • depression
- 977 • headache
- 978 • tiredness
- 979 • dizziness
- 980 • nausea
- 981 • diarrhea
- 982 • rash
- 983 • fever

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

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

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

990 **How should I store EPZICOM?**

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

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

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

994 **EPZICOM does not stop you from spreading HIV to other people by sex,**  
995 **sharing needles, or being exposed to your blood.** Talk with your healthcare  
996 provider about safe sexual practices that protect your partner. Never share needles.

997 Do not share personal items that can have blood or body fluids on them, like  
998 toothbrushes or razor blades.

999 Medicines are sometimes prescribed for purposes other than those listed in a  
1000 Medication Guide. Do not use EPZICOM for a condition for which it was not  
1001 prescribed. Do not give EPZICOM to other people, even if they have the same  
1002 symptoms that you have. It may harm them.

1003 This Medication Guide summarizes the most important information about EPZICOM.  
1004 If you would like more information, talk with your healthcare provider. You can ask  
1005 your healthcare provider or pharmacist for the information about EPZICOM that is  
1006 written for healthcare professionals.

1007 For more information go to [www.EPZICOM.com](http://www.EPZICOM.com) or call 1-877-844-8872.

1008 **What are the ingredients in EPZICOM?**

1009 Active ingredients: abacavir sulfate and lamivudine

1010 Inactive ingredients: magnesium stearate, microcrystalline cellulose, sodium starch  
1011 glycolate, and OPADRY® orange YS-1-13065-A, a film coating made of FD&C Yellow  
1012 No. 6, hypromellose, polyethylene glycol 400, polysorbate 80, and titanium dioxide.

1013 COMBIVIR, EPIVIR, EPZICOM, TRIZIVIR, and ZIAGEN are registered trademarks of  
1014 ViiV Healthcare.

1015 The brands listed are trademarks of their respective owners and are not trademarks  
1016 of ViiV Healthcare. The makers of these brands are not affiliated with and do not  
1017 endorse ViiV Healthcare or its products.

1018

1019

1020 Manufactured for:



1021

1022 ViiV Healthcare

1023 Research Triangle Park, NC 27709

1024 by:



1025  
1026 GlaxoSmithKline  
1027 Research Triangle Park, NC 27709  
  
1028 Lamivudine is manufactured under agreement from  
1029 **Shire Pharmaceuticals Group plc**  
1030 Basingstoke, UK  
  
1031 This Medication Guide has been approved by the US Food and Drug Administration.  
  
1032  
1033 ©2011, ViiV Healthcare. All rights reserved.  
1034  
1035 February 2011  
1036 EPZ: 5MG  
1037