

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

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

ZIAGEN® (abacavir sulfate) Tablets and Oral Solution  
Initial U.S. Approval: 1998

**WARNING: HYPERSENSITIVITY REACTIONS/LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY**

See full prescribing information for complete boxed warning.

- Serious and sometimes fatal hypersensitivity reactions have been associated with ZIAGEN (abacavir sulfate). (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 ZIAGEN as soon as a hypersensitivity reaction is suspected. Regardless of HLA-B\*5701 status, permanently discontinue ZIAGEN if hypersensitivity cannot be ruled out, even when other diagnoses are possible. (5.1)
- Following a hypersensitivity reaction to abacavir, NEVER restart ZIAGEN 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)

**RECENT MAJOR CHANGES**

Boxed Warning	July 2008
Dosage and Administration (2.2)	Month year
Warnings and Precautions (5.1, 5.5)	July 2008

**INDICATIONS AND USAGE**

ZIAGEN, a nucleoside analogue, 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: 600 mg daily, administered as either 300 mg twice daily or 600 mg once daily. (2.1)
- Pediatric Patients Aged 3 Months and Older: Dose should be calculated on body weight (kg) and should not exceed 300 mg twice daily. (2.2)

- Patients With Hepatic Impairment: Mild hepatic impairment – 200 mg twice daily; moderate/severe hepatic impairment – contraindicated. (2.3)

**DOSAGE FORMS AND STRENGTHS**

Tablets: 300 mg, scored; Oral Solution: 20 mg/mL (3)

**CONTRAINDICATIONS**

- Previously demonstrated hypersensitivity to abacavir. (4, 5.1)
- Moderate or severe hepatic impairment. (4)

**WARNINGS AND PRECAUTIONS**

- Hypersensitivity: Serious and sometimes fatal hypersensitivity reactions have been associated with ZIAGEN and other abacavir-containing products. Read full prescribing information section 5.1 before prescribing ZIAGEN. (5.1)
- Lactic acidosis and severe hepatomegaly with steatosis have been reported with the use of nucleoside analogues. (5.2)
- Immune reconstitution syndrome (5.3) and redistribution/accumulation of body fat have been reported in patients treated with combination antiretroviral therapy. (5.4)

**ADVERSE REACTIONS**

- The most commonly reported adverse reactions of at least moderate intensity (incidence ≥10%) in adult HIV-1 clinical studies were nausea, headache, malaise and fatigue, nausea and vomiting, and dreams/sleep disorders. (6.1)
- The most commonly reported adverse reactions of at least moderate intensity (incidence ≥5%) in pediatric HIV-1 clinical studies were fever and/or chills, nausea and vomiting, skin rashes, and ear/nose/throat infections. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 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)
- Methadone: An increased methadone dose may be required in a small number of patients. (7)

See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE.

Revised: Month 200x  
ZGN:xPI

**FULL PRESCRIBING INFORMATION: CONTENTS\***

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

**1 INDICATIONS AND USAGE**

**2 DOSAGE AND ADMINISTRATION**

- 2.1 Adult Patients
- 2.2 Pediatric Patients
- 2.3 Patients with Hepatic Impairment

**3 DOSAGE FORMS AND STRENGTHS**

**4 CONTRAINDICATIONS**

**5 WARNINGS AND PRECAUTIONS**

- 5.1 Hypersensitivity Reaction
- 5.2 Lactic Acidosis/Severe Hepatomegaly With Steatosis
- 5.3 Immune Reconstitution Syndrome
- 5.4 Fat Redistribution
- 5.5 Myocardial Infarction

**6 ADVERSE REACTIONS**

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

**7 DRUG INTERACTIONS**

**8 USE IN SPECIFIC POPULATIONS**

- 8.1 Pregnancy

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

**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**

- 14.1 Adults
- 14.2 Pediatric Patients

**15 REFERENCES**

**16 HOW SUPPLIED/STORAGE AND HANDLING**

**17 PATIENT COUNSELING INFORMATION**

- 17.1 Information About Therapy With ZIAGEN
- 17.2 FDA Approved Patient Labeling

\*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**

4 **Serious and sometimes fatal hypersensitivity reactions have been associated with**  
5 **ZIAGEN (abacavir sulfate).**

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

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

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

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

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

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

32 **1 INDICATIONS AND USAGE**

33 **ZIAGEN Tablets and Oral Solution, in combination with other antiretroviral agents, are**  
34 **indicated for the treatment of human immunodeficiency virus (HIV-1) infection.**

35 **Additional important information on the use of ZIAGEN for treatment of HIV-1**  
36 **infection:**

- ZIAGEN is one of multiple products containing abacavir. Before starting ZIAGEN, review medical history for prior exposure to any abacavir-containing product in order to avoid reintroduction in a patient with a history of hypersensitivity to abacavir.

## 2 DOSAGE AND ADMINISTRATION

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

### 2.1 Adult Patients

The recommended oral dose of ZIAGEN for adults is 600 mg daily, administered as either 300 mg twice daily or 600 mg once daily, in combination with other antiretroviral agents.

### 2.2 Pediatric Patients

The recommended oral dose of ZIAGEN Oral Solution in HIV-1-infected pediatric patients aged 3 months and older is 8 mg/kg twice daily (up to a maximum of 300 mg twice daily) in combination with other antiretroviral agents.

ZIAGEN is also available as a scored tablet for HIV-1-infected pediatric patients weighing greater than or equal to 14 kg for whom a solid dosage form is appropriate. Before prescribing ZIAGEN Tablets, children should be assessed for the ability to swallow tablets. If a child is unable to reliably swallow ZIAGEN Tablets, the oral solution formulation should be prescribed. The recommended oral dosage of ZIAGEN Tablets for HIV-1-infected pediatric patients is presented in Table 1.

**Table 1. Dosing Recommendations for ZIAGEN Tablets in Pediatric Patients**

Weight (kg)	Dosage Regimen Using Scored Tablet		Total Daily Dose
	AM Dose	PM Dose	
14 to 21	½ tablet (150 mg)	½ tablet (150 mg)	300 mg
>21 to <30	½ tablet (150 mg)	1 tablet (300 mg)	450 mg
≥30	1 tablet (300 mg)	1 tablet (300 mg)	600 mg

### 2.3 Patients with Hepatic Impairment

The recommended dose of ZIAGEN in patients with mild hepatic impairment (Child-Pugh score 5 to 6) is 200 mg twice daily. To enable dose reduction, ZIAGEN Oral Solution (10 mL twice daily) should be used for the treatment of these patients. The safety, efficacy, and pharmacokinetic properties of abacavir have not been established in patients with moderate to severe hepatic impairment; therefore, ZIAGEN is contraindicated in these patients.

69 **3 DOSAGE FORMS AND STRENGTHS**

70 ZIAGEN Tablets, containing abacavir sulfate equivalent to 300 mg abacavir, are yellow,  
71 biconvex, scored, capsule-shaped, film-coated, and imprinted with “GX 623” on both sides.

72 ZIAGEN Oral Solution, each mL containing abacavir sulfate equivalent to 20 mg of  
73 abacavir, is a clear to opalescent, yellowish, strawberry-banana-flavored liquid.

74 **4 CONTRAINDICATIONS**

75 ZIAGEN is contraindicated in patients with previously demonstrated hypersensitivity to  
76 abacavir or any other component of the products. NEVER restart ZIAGEN or any other  
77 abacavir-containing product following a hypersensitivity reaction to abacavir, regardless of  
78 HLA-B\*5701 status [*see Warnings and Precautions (5.1), Adverse Reactions (6)*].

79 ZIAGEN is contraindicated in patients with moderate or severe hepatic impairment.

80 **5 WARNINGS AND PRECAUTIONS**

81 **5.1 Hypersensitivity Reaction**

82 Serious and sometimes fatal hypersensitivity reactions have been associated with  
83 ZIAGEN and other abacavir-containing products. Patients who carry the HLA-B\*5701 allele are  
84 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 ZIAGEN if hypersensitivity cannot  
94 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)

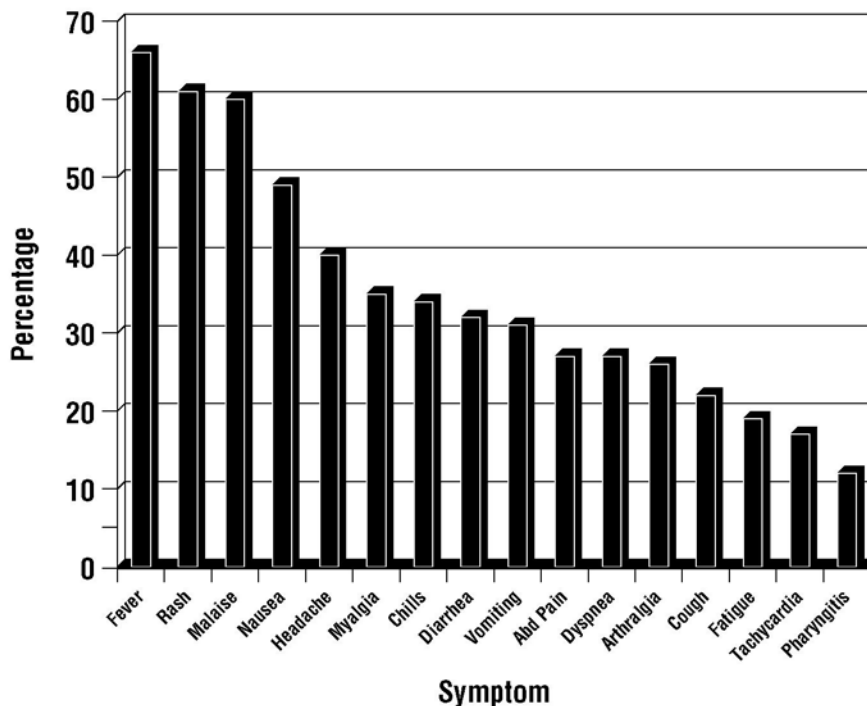
103 Group 4: Constitutional (including generalized malaise, fatigue, or achiness)

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 patients  
108 (n = 206) in 9 clinical trials (range: 2% to 9%) with enrollment from November 1999 to February  
109 2002. Data on time to onset and symptoms of suspected hypersensitivity were collected on a  
110 detailed data collection module. The frequencies of symptoms are shown in Figure 1. Symptoms  
111 usually appeared within the first 6 weeks of treatment with abacavir, although the reaction may  
112 occur at any time during therapy. Median time to onset was 9 days; 89% appeared within the first  
113 6 weeks; 95% of patients reported symptoms from 2 or more of the 5 groups listed above.  
114

115 **Figure 1. Hypersensitivity-Related Symptoms Reported With**  
116 **≥10% Frequency in Clinical Trials (n = 206 Patients)**



117  
118

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

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

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

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

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

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

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

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

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

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

168 Screening for carriage of the HLA-B\*5701 allele is recommended prior to initiating  
169 treatment with abacavir. Screening is also recommended prior to reinitiation of abacavir in  
170 patients of unknown HLA-B\*5701 status who have previously tolerated abacavir. For

171 HLA-B\*5701-positive patients, initiating or reinitiating treatment with an abacavir-containing  
172 regimen is not recommended and should be considered only with close medical supervision and  
173 under exceptional circumstances where potential benefit outweighs the risk.

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

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

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

## 184 **5.2 Lactic Acidosis/Severe Hepatomegaly With Steatosis**

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

## 194 **5.3 Immune Reconstitution Syndrome**

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

## 201 **5.4 Fat Redistribution**

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

## 207 **5.5 Myocardial Infarction**

208 In a published prospective, observational, epidemiological study designed to investigate  
209 the rate of myocardial infarction in patients on combination antiretroviral therapy, the use of  
210 abacavir within the previous 6 months was correlated with an increased risk of myocardial

211 infarction (MI).<sup>1</sup> In a sponsor-conducted pooled analysis of clinical trials, no excess risk of  
212 myocardial infarction was observed in abacavir-treated subjects as compared with control  
213 subjects. In totality, the available data from the observational cohort and from clinical trials are  
214 inconclusive.

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

## 218 **6 ADVERSE REACTIONS**

- 219 • Serious and sometimes fatal hypersensitivity reactions have been associated with ZIAGEN  
220 (abacavir sulfate). In one study, once-daily dosing of ZIAGEN was associated with more  
221 severe hypersensitivity reactions [*see Warnings and Precautions (5.1)*].

### 222 **6.1 Clinical Trials Experience**

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

226 Adults: Therapy-Naive Adults: Treatment-emergent clinical adverse reactions (rated by  
227 the investigator as moderate or severe) with a greater than or equal to 5% frequency during  
228 therapy with ZIAGEN 300 mg twice daily, lamivudine 150 mg twice daily, and efavirenz  
229 600 mg daily compared with zidovudine 300 mg twice daily, lamivudine 150 mg twice daily,  
230 and efavirenz 600 mg daily from CNA30024 are listed in Table 2.  
231

232 **Table 2. Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate**  
 233 **Intensity (Grades 2-4, ≥5% Frequency) in Therapy-Naive Adults (CNA30024<sup>\*</sup>) Through**  
 234 **48 Weeks of Treatment**

Adverse Reaction	ZIAGEN plus Lamivudine plus Efavirenz (n = 324)	Zidovudine plus Lamivudine plus Efavirenz (n = 325)
Dreams/sleep disorders	10%	10%
Drug hypersensitivity	9%	<1% <sup>†</sup>
Headaches/migraine	7%	11%
Nausea	7%	11%
Fatigue/malaise	7%	10%
Diarrhea	7%	6%
Rashes	6%	12%
Abdominal pain/gastritis/ gastrointestinal signs and symptoms	6%	8%
Depressive disorders	6%	6%
Dizziness	6%	6%
Musculoskeletal pain	6%	5%
Bronchitis	4%	5%
Vomiting	2%	9%

235 <sup>\*</sup> This study used double-blind ascertainment of suspected hypersensitivity reactions. During  
 236 the blinded portion of the study, suspected hypersensitivity to abacavir was reported by  
 237 investigators in 9% of 324 patients in the abacavir group and 3% of 325 patients in the  
 238 zidovudine group.

239 <sup>†</sup> Ten (3%) cases of suspected drug hypersensitivity were reclassified as not being due to  
 240 abacavir following unblinding.

241  
 242 Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or  
 243 severe) with a greater than or equal to 5% frequency during therapy with ZIAGEN 300 mg twice  
 244 daily, lamivudine 150 mg twice daily, and zidovudine 300 mg twice daily compared with  
 245 indinavir 800 mg 3 times daily, lamivudine 150 mg twice daily, and zidovudine 300 mg twice  
 246 daily from CNA3005 are listed in Table 3.

247

248 **Table 3. Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate**  
 249 **Intensity (Grades 2-4, ≥5% Frequency) in Therapy-Naive Adults (CNA3005) Through**  
 250 **48 Weeks of Treatment**

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

251

252 Five patients receiving ZIAGEN in CNA3005 experienced worsening of pre-existing  
 253 depression compared with none in the indinavir arm. The background rates of pre-existing  
 254 depression were similar in the 2 treatment arms.

255 *ZIAGEN Once Daily Versus ZIAGEN Twice Daily (CNA30021):*

256 Treatment-emergent clinical adverse reactions (rated by the investigator as at least moderate)  
 257 with a greater than or equal to 5% frequency during therapy with ZIAGEN 600 mg once daily or  
 258 ZIAGEN 300 mg twice daily both in combination with lamivudine 300 mg once daily and  
 259 efavirenz 600 mg once daily from CNA30021 were similar. For hypersensitivity reactions,  
 260 patients receiving ZIAGEN once daily showed a rate of 9% in comparison with a rate of 7% for  
 261 patients receiving ZIAGEN twice daily. However, patients receiving ZIAGEN 600 mg once  
 262 daily, experienced a significantly higher incidence of severe drug hypersensitivity reactions and  
 263 severe diarrhea compared with patients who received ZIAGEN 300 mg twice daily. Five percent  
 264 (5%) of patients receiving ZIAGEN 600 mg once daily had severe drug hypersensitivity  
 265 reactions compared with 2% of patients receiving ZIAGEN 300 mg twice daily. Two percent  
 266 (2%) of patients receiving ZIAGEN 600 mg once daily had severe diarrhea while none of the  
 267 patients receiving ZIAGEN 300 mg twice daily had this event.

268 *Laboratory Abnormalities:* Laboratory abnormalities (Grades 3-4) in therapy-naive  
 269 adults during therapy with ZIAGEN 300 mg twice daily, lamivudine 150 mg twice daily, and

270 efavirenz 600 mg daily compared with zidovudine 300 mg twice daily, lamivudine 150 mg twice  
271 daily, and efavirenz 600 mg daily from CNA30024 are listed in Table 4.

272

273 **Table 4. Laboratory Abnormalities (Grades 3-4) in Therapy-Naive Adults (CNA30024)**  
274 **Through 48 Weeks of Treatment**

Grade 3/4 Laboratory Abnormalities	ZIAGEN plus Lamivudine plus Efavirenz (n = 324)	Zidovudine plus Lamivudine plus Efavirenz (n = 325)
Elevated CPK (>4 X ULN)	8%	8%
Elevated ALT (>5 X ULN)	6%	6%
Elevated AST (>5 X ULN)	6%	5%
Hypertriglyceridemia (>750 mg/dL)	6%	5%
Hyperamylasemia (>2 X ULN)	4%	5%
Neutropenia (ANC <750/mm <sup>3</sup> )	2%	4%
Anemia (Hgb ≤6.9 gm/dL)	<1%	2%
Thrombocytopenia (Platelets <50,000/mm <sup>3</sup> )	1%	<1%
Leukopenia (WBC ≤1,500/mm <sup>3</sup> )	<1%	2%

275 ULN = Upper limit of normal.

276 n = Number of patients assessed.

277

278 Laboratory abnormalities in CNA3005 are listed in Table 5.

279

280 **Table 5. Treatment-Emergent Laboratory Abnormalities (Grades 3-4) in CNA3005**

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

281 ULN = Upper limit of normal.

282 n = Number of patients assessed.

283

284 The frequencies of treatment-emergent laboratory abnormalities were comparable  
285 between treatment groups in CNA30021.

286 Pediatric Patients: Therapy-Experienced Pediatric Patients: Treatment-emergent  
287 clinical adverse reactions (rated by the investigator as moderate or severe) with a greater than or  
288 equal to 5% frequency during therapy with ZIAGEN 8 mg/kg twice daily, lamivudine 4 mg/kg  
289 twice daily, and zidovudine 180 mg/m<sup>2</sup> twice daily compared with lamivudine 4 mg/kg twice  
290 daily and zidovudine 180 mg/m<sup>2</sup> twice daily from CNA3006 are listed in Table 6.

291

292 **Table 6. Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate**  
293 **Intensity (Grades 2-4, ≥5% Frequency) in Therapy-Experienced Pediatric Patients**  
294 **(CNA3006) Through 16 Weeks of Treatment**

Adverse Reaction	ZIAGEN plus Lamivudine plus Zidovudine (n = 102)	Lamivudine plus Zidovudine (n = 103)
Fever and/or chills	9%	7%
Nausea and vomiting	9%	2%
Skin rashes	7%	1%
Ear/nose/throat infections	5%	1%
Pneumonia	4%	5%
Headache	1%	5%

295

296 Laboratory Abnormalities: In Study CNA3006, laboratory abnormalities (anemia,  
297 neutropenia, liver function test abnormalities, and CPK elevations) were observed with similar  
298 frequencies as in a study of therapy-naive adults (CNA30024). Mild elevations of blood glucose  
299 were more frequent in pediatric patients receiving ZIAGEN (CNA3006) as compared with adult  
300 patients (CNA30024).

301 Other Adverse Events: In addition to adverse reactions and laboratory abnormalities  
302 reported in Tables 2, 3, 4, 5, and 6, other adverse reactions observed in the expanded access  
303 program were pancreatitis and increased GGT.

## 304 **6.2 Postmarketing Experience**

305 In addition to adverse reactions reported from clinical trials, the following reactions have  
306 been identified during postmarketing use of ZIAGEN. Because they are reported voluntarily  
307 from a population of unknown size, estimates of frequency cannot be made. These reactions have  
308 been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or  
309 potential causal connection to ZIAGEN.

310 Body as a Whole: Redistribution/accumulation of body fat.

311 Cardiovascular: Myocardial infarction.

312 Hepatic: Lactic acidosis and hepatic steatosis.

313 Skin: Suspected Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)  
314 have been reported in patients receiving abacavir primarily in combination with medications

315 known to be associated with SJS and TEN, respectively. Because of the overlap of clinical signs  
316 and symptoms between hypersensitivity to abacavir and SJS and TEN, and the possibility of  
317 multiple drug sensitivities in some patients, abacavir should be discontinued and not restarted in  
318 such cases.

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

## 320 **7 DRUG INTERACTIONS**

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

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

## 330 **8 USE IN SPECIFIC POPULATIONS**

### 331 **8.1 Pregnancy**

332 Pregnancy Category C. Studies in pregnant rats showed that abacavir is transferred to the  
333 fetus through the placenta. Fetal malformations (increased incidences of fetal anasarca and  
334 skeletal malformations) and developmental toxicity (depressed fetal body weight and reduced  
335 crown-rump length) were observed in rats at a dose which produced 35 times the human  
336 exposure, based on AUC. Embryonic and fetal toxicities (increased resorptions, decreased fetal  
337 body weights) and toxicities to the offspring (increased incidence of stillbirth and lower body  
338 weights) occurred at half of the above-mentioned dose in separate fertility studies conducted in  
339 rats. In the rabbit, no developmental toxicity and no increases in fetal malformations occurred at  
340 doses that produced 8.5 times the human exposure at the recommended dose based on AUC.

341 There are no adequate and well-controlled studies in pregnant women. ZIAGEN should  
342 be used during pregnancy only if the potential benefits outweigh the risk.

343 Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant  
344 women exposed to ZIAGEN, an Antiretroviral Pregnancy Registry has been established.  
345 Physicians are encouraged to register patients by calling 1-800-258-4263.

### 346 **8.3 Nursing Mothers**

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

349 Although it is not known if abacavir is excreted in human milk, abacavir is secreted into  
350 the milk of lactating rats. Because of both the potential for HIV-1 transmission and the potential  
351 for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if  
352 they are receiving ZIAGEN.

### 353 **8.4 Pediatric Use**

354 The safety and effectiveness of ZIAGEN have been established in pediatric patients  
355 3 months to 13 years of age. Use of ZIAGEN in these age groups is supported by  
356 pharmacokinetic studies and evidence from adequate and well-controlled studies of ZIAGEN in  
357 adults and pediatric patients [see *Dosage and Administration (2.2)*, *Clinical Pharmacology*  
358 *(12.3)*, *Clinical Studies (14.2)*].

### 359 **8.5 Geriatric Use**

360 Clinical studies of ZIAGEN did not include sufficient numbers of patients aged 65 and  
361 over to determine whether they respond differently from younger patients. In general, dose  
362 selection for an elderly patient should be cautious, reflecting the greater frequency of decreased  
363 hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

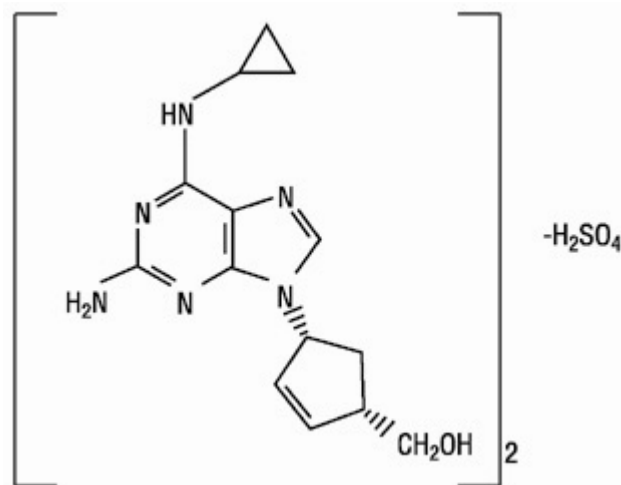
## 364 **10 OVERDOSAGE**

365 There is no known antidote for ZIAGEN. It is not known whether abacavir can be  
366 removed by peritoneal dialysis or hemodialysis.

## 367 **11 DESCRIPTION**

368 ZIAGEN is the brand name for abacavir sulfate, a synthetic carbocyclic nucleoside  
369 analogue with inhibitory activity against HIV-1. The chemical name of abacavir sulfate is  
370 (1*S*,*cis*)-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate  
371 (salt) (2:1). Abacavir sulfate is the enantiomer with 1*S*, 4*R* absolute configuration on the  
372 cyclopentene ring. It has a molecular formula of  $(C_{14}H_{18}N_6O)_2 \cdot H_2SO_4$  and a molecular weight of  
373 670.76 daltons. It has the following structural formula:

374



375

376

377 Abacavir sulfate is a white to off-white solid with a solubility of approximately  
378 77 mg/mL in distilled water at 25°C. It has an octanol/water (pH 7.1 to 7.3) partition coefficient  
379 (log *P*) of approximately 1.20 at 25°C.

380 ZIAGEN Tablets are for oral administration. Each tablet contains abacavir sulfate  
381 equivalent to 300 mg of abacavir as active ingredient and the following inactive ingredients:

382 colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, and sodium starch  
383 glycolate. The tablets are coated with a film that is made of hypromellose, polysorbate 80,  
384 synthetic yellow iron oxide, titanium dioxide, and triacetin.

385 ZIAGEN Oral Solution is for oral administration. Each milliliter (1 mL) of ZIAGEN Oral  
386 Solution contains abacavir sulfate equivalent to 20 mg of abacavir (i.e., 20 mg/mL) as active  
387 ingredient and the following inactive ingredients: artificial strawberry and banana flavors, citric  
388 acid (anhydrous), methylparaben and propylparaben (added as preservatives), propylene glycol,  
389 saccharin sodium, sodium citrate (dihydrate), sorbitol solution, and water.

390 In vivo, abacavir sulfate dissociates to its free base, abacavir. All dosages for ZIAGEN  
391 are expressed in terms of abacavir.

## 392 **12 CLINICAL PHARMACOLOGY**

### 393 **12.1 Mechanism of Action**

394 Abacavir is an antiviral agent [*See Clinical Pharmacology (12.4)*].

### 395 **12.3 Pharmacokinetics**

396 Pharmacokinetics in Adults: The pharmacokinetic properties of abacavir have been  
397 studied in asymptomatic, HIV-1-infected adult patients after administration of a single  
398 intravenous (IV) dose of 150 mg and after single and multiple oral doses. The pharmacokinetic  
399 properties of abacavir were independent of dose over the range of 300 to 1,200 mg/day.

400 *Absorption and Bioavailability:* Abacavir was rapidly and extensively absorbed after  
401 oral administration. The geometric mean absolute bioavailability of the tablet was 83%. After  
402 oral administration of 300 mg twice daily in 20 patients, the steady-state peak serum abacavir  
403 concentration ( $C_{max}$ ) was  $3.0 \pm 0.89$  mcg/mL (mean  $\pm$  SD) and  $AUC_{(0-12\text{ hr})}$  was  
404  $6.02 \pm 1.73$  mcg•hr/mL. After oral administration of a single dose of 600 mg of abacavir in  
405 20 patients,  $C_{max}$  was  $4.26 \pm 1.19$  mcg/mL (mean  $\pm$  SD) and  $AUC_{\infty}$  was  
406  $11.95 \pm 2.51$  mcg•hr/mL.

407 *Distribution:* The apparent volume of distribution after IV administration of abacavir  
408 was  $0.86 \pm 0.15$  L/kg, suggesting that abacavir distributes into extravascular space. In 3 subjects,  
409 the CSF  $AUC_{(0-6\text{ hr})}$  to plasma abacavir  $AUC_{(0-6\text{ hr})}$  ratio ranged from 27% to 33%.

410 Binding of abacavir to human plasma proteins is approximately 50%. Binding of abacavir  
411 to plasma proteins was independent of concentration. Total blood and plasma drug-related  
412 radioactivity concentrations are identical, demonstrating that abacavir readily distributes into  
413 erythrocytes.

414 *Metabolism:* In humans, abacavir is not significantly metabolized by cytochrome  
415 P450 enzymes. The primary routes of elimination of abacavir are metabolism by alcohol  
416 dehydrogenase (to form the 5'-carboxylic acid) and glucuronyl transferase (to form the  
417 5'-glucuronide). The metabolites do not have antiviral activity. In vitro experiments reveal that  
418 abacavir does not inhibit human CYP3A4, CYP2D6, or CYP2C9 activity at clinically relevant  
419 concentrations.

420 *Elimination:* Elimination of abacavir was quantified in a mass balance study following  
421 administration of a 600-mg dose of <sup>14</sup>C-abacavir: 99% of the radioactivity was recovered, 1.2%  
422 was excreted in the urine as abacavir, 30% as the 5'-carboxylic acid metabolite, 36% as the  
423 5'-glucuronide metabolite, and 15% as unidentified minor metabolites in the urine. Fecal  
424 elimination accounted for 16% of the dose.

425 In single-dose studies, the observed elimination half-life ( $t_{1/2}$ ) was  $1.54 \pm 0.63$  hours.  
426 After intravenous administration, total clearance was  $0.80 \pm 0.24$  L/hr/kg (mean  $\pm$  SD).

427 Effects of Food on Oral Absorption: Bioavailability of abacavir tablets was assessed in  
428 the fasting and fed states. There was no significant difference in systemic exposure ( $AUC_{\infty}$ ) in  
429 the fed and fasting states; therefore, ZIAGEN Tablets may be administered with or without food.  
430 Systemic exposure to abacavir was comparable after administration of ZIAGEN Oral Solution  
431 and ZIAGEN Tablets. Therefore, these products may be used interchangeably.

432 Special Populations: Renal Impairment: The pharmacokinetic properties of ZIAGEN  
433 have not been determined in patients with impaired renal function. Renal excretion of unchanged  
434 abacavir is a minor route of elimination in humans.

435 *Hepatic Impairment:* The pharmacokinetics of abacavir have been studied in patients  
436 with mild hepatic impairment (Child-Pugh score 5 to 6). Results showed that there was a mean  
437 increase of 89% in the abacavir AUC, and an increase of 58% in the half-life of abacavir after a  
438 single dose of 600 mg of abacavir. The AUCs of the metabolites were not modified by mild liver  
439 disease; however, the rates of formation and elimination of the metabolites were decreased. A  
440 dose of 200 mg (provided by 10 mL of ZIAGEN Oral Solution) administered twice daily is  
441 recommended for patients with mild liver disease. The safety, efficacy, and pharmacokinetics of  
442 abacavir have not been studied in patients with moderate or severe hepatic impairment, therefore  
443 ZIAGEN is contraindicated in these patients.

444 *Pediatric Patients:* The pharmacokinetics of abacavir have been studied after either  
445 single or repeat doses of ZIAGEN in 68 pediatric patients. Following multiple-dose  
446 administration of ZIAGEN 8 mg/kg twice daily, steady-state  $AUC_{(0-12 \text{ hr})}$  and  $C_{\text{max}}$  were  
447  $9.8 \pm 4.56$  mcg•hr/mL and  $3.71 \pm 1.36$  mcg/mL (mean  $\pm$  SD), respectively [see *Use in Specific*  
448 *Populations (8.4)*]. In addition, to support dosing of ZIAGEN scored tablet (300 mg) for  
449 pediatric patients 14 to greater than 30 kg, analysis of actual and simulated pharmacokinetic data  
450 indicated comparable exposures are expected following administration of 300 mg scored tablet  
451 and the 8 mg/kg dosing regimen using oral solution.

452 *Geriatric Patients:* The pharmacokinetics of ZIAGEN have not been studied in  
453 patients over 65 years of age.

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

457 *Race:* There are no significant differences between blacks and Caucasians in abacavir  
458 pharmacokinetics.

459 Drug Interactions: In human liver microsomes, abacavir did not inhibit cytochrome  
460 P450 isoforms (2C9, 2D6, 3A4). Based on these data, it is unlikely that clinically significant  
461 drug interactions will occur between abacavir and drugs metabolized through these pathways.

462 *Lamivudine and/or Zidovudine:* Due to the common metabolic pathways of abacavir  
463 and zidovudine via glucuronyl transferase, 15 HIV-1-infected patients were enrolled in a  
464 crossover study evaluating single doses of abacavir (600 mg), lamivudine (150 mg), and  
465 zidovudine (300 mg) alone or in combination. Analysis showed no clinically relevant changes in  
466 the pharmacokinetics of abacavir with the addition of lamivudine or zidovudine or the  
467 combination of lamivudine and zidovudine. Lamivudine exposure (AUC decreased 15%) and  
468 zidovudine exposure (AUC increased 10%) did not show clinically relevant changes with  
469 concurrent abacavir.

470 *Ethanol:* Due to their common metabolic pathways via alcohol dehydrogenase, the  
471 pharmacokinetic interaction between abacavir and ethanol was studied in 24 HIV-1-infected  
472 male patients. Each patient received the following treatments on separate occasions: a single  
473 600-mg dose of abacavir, 0.7 g/kg ethanol (equivalent to 5 alcoholic drinks), and abacavir  
474 600 mg plus 0.7 g/kg ethanol. Coadministration of ethanol and abacavir resulted in a 41%  
475 increase in abacavir  $AUC_{\infty}$  and a 26% increase in abacavir  $t_{1/2}$ . In males, abacavir had no effect  
476 on the pharmacokinetic properties of ethanol, so no clinically significant interaction is expected  
477 in men. This interaction has not been studied in females.

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

#### 484 **12.4 Microbiology**

485 Abacavir is a carbocyclic synthetic nucleoside analogue. Abacavir is converted by  
486 cellular enzymes to the active metabolite, carbovir triphosphate (CBV-TP), an analogue of  
487 deoxyguanosine-5'-triphosphate (dGTP). CBV-TP inhibits the activity of HIV-1 reverse  
488 transcriptase (RT) both by competing with the natural substrate dGTP and by its incorporation  
489 into viral DNA. The lack of a 3'-OH group in the incorporated nucleotide analogue prevents the  
490 formation of the 5' to 3' phosphodiester linkage essential for DNA chain elongation, and  
491 therefore, the viral DNA growth is terminated. CBV-TP is a weak inhibitor of cellular DNA  
492 polymerases  $\alpha$ ,  $\beta$ , and  $\gamma$ .

493 Antiviral Activity: The antiviral activity of abacavir against HIV-1 was evaluated against  
494 a T-cell tropic laboratory strain HIV-1<sub>IIIB</sub> in lymphoblastic cell lines, a monocyte/macrophage  
495 tropic laboratory strain HIV-1<sub>BaL</sub> in primary monocytes/macrophages, and clinical isolates in  
496 peripheral blood mononuclear cells. The concentration of drug necessary to effect viral  
497 replication by 50 percent ( $EC_{50}$ ) ranged from 3.7 to 5.8  $\mu$ M (1  $\mu$ M = 0.28 mcg/mL) and 0.07 to  
498 1.0  $\mu$ M against HIV-1<sub>IIIB</sub> and HIV-1<sub>BaL</sub>, respectively, and was  $0.26 \pm 0.18 \mu$ M against 8 clinical

499 isolates. The EC<sub>50</sub> values of abacavir against different HIV-1 clades (A-G) ranged from 0.0015  
500 to 1.05 μM, and against HIV-2 isolates, from 0.024 to 0.49 μM. Abacavir had synergistic  
501 activity in cell culture in combination with the nucleoside reverse transcriptase inhibitor (NRTI)  
502 zidovudine, the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, and the  
503 protease inhibitor (PI) amprenavir; and additive activity in combination with the NRTIs  
504 didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine. Ribavirin (50 μM)  
505 had no effect on the anti-HIV-1 activity of abacavir in cell culture.

506 **Resistance:** HIV-1 isolates with reduced susceptibility to abacavir have been selected in  
507 cell culture and were also obtained from patients treated with abacavir. Genotypic analysis of  
508 isolates selected in cell culture and recovered from abacavir-treated patients demonstrated that  
509 amino acid substitutions K65R, L74V, Y115F, and M184V/I in RT contributed to abacavir  
510 resistance. In a study of therapy-naïve adults receiving ZIAGEN 600 mg once daily (n = 384) or  
511 300 mg twice daily (n = 386), in a background regimen of lamivudine 300 mg once daily and  
512 efavirenz 600 mg once daily (CNA30021), the incidence of virologic failure at 48 weeks was  
513 similar between the 2 groups (11% in both arms). Genotypic (n = 38) and phenotypic analyses  
514 (n = 35) of virologic failure isolates from this study showed that the RT substitutions that  
515 emerged during abacavir once-daily and twice-daily therapy were K65R, L74V, Y115F, and  
516 M184V/I. The substitution M184V/I was the most commonly observed substitution in virologic  
517 failure isolates from patients receiving abacavir once daily (56%, 10/18) and twice daily (40%,  
518 8/20).

519 Thirty-nine percent (7/18) of the isolates from patients who experienced virologic failure  
520 in the abacavir once-daily arm had a greater than 2.5-fold decrease in abacavir susceptibility with  
521 a median-fold decrease of 1.3 (range 0.5 to 11) compared with 29% (5/17) of the failure isolates  
522 in the twice-daily arm with a median-fold decrease of 0.92 (range 0.7 to 13).

523 **Cross-Resistance:** Cross-resistance has been observed among NRTIs. Isolates  
524 containing abacavir resistance-associated substitutions, namely, K65R, L74V, Y115F, and  
525 M184V, exhibited cross-resistance to didanosine, emtricitabine, lamivudine, tenofovir, and  
526 zalcitabine in cell culture and in patients. The K65R substitution can confer resistance to  
527 abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine; the L74V  
528 substitution can confer resistance to abacavir, didanosine, and zalcitabine; and the M184V  
529 substitution can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, and  
530 zalcitabine. An increasing number of thymidine analogue mutations (TAMs: M41L, D67N,  
531 K70R, L210W, T215Y/F, K219E/R/H/Q/N) is associated with a progressive reduction in  
532 abacavir susceptibility.

## 533 **13 NONCLINICAL TOXICOLOGY**

### 534 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

535 Abacavir was administered orally at 3 dosage levels to separate groups of mice and rats  
536 in 2-year carcinogenicity studies. Results showed an increase in the incidence of malignant and  
537 non-malignant tumors. Malignant tumors occurred in the preputial gland of males and the clitoral

538 gland of females of both species, and in the liver of female rats. In addition, non-malignant  
539 tumors also occurred in the liver and thyroid gland of female rats. These observations were made  
540 at systemic exposures in the range of 6 to 32 times the human exposure at the recommended  
541 dose. It is not known how predictive the results of rodent carcinogenicity studies may be for  
542 humans.

543 Abacavir induced chromosomal aberrations both in the presence and absence of  
544 metabolic activation in an in vitro cytogenetic study in human lymphocytes. Abacavir was  
545 mutagenic in the absence of metabolic activation, although it was not mutagenic in the presence  
546 of metabolic activation in an L5178Y mouse lymphoma assay. Abacavir was clastogenic in  
547 males and not clastogenic in females in an in vivo mouse bone marrow micronucleus assay.

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

550 Abacavir had no adverse effects on the mating performance or fertility of male and  
551 female rats at a dose approximately 8 times the human exposure at the recommended dose based  
552 on body surface area comparisons.

### 553 **13.2 Animal Toxicology and/or Pharmacology**

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

## 557 **14 CLINICAL STUDIES**

### 558 **14.1 Adults**

559 Therapy-Naive Adults: CNA30024 was a multicenter, double-blind, controlled study in  
560 which 649 HIV-1-infected, therapy-naive adults were randomized and received either ZIAGEN  
561 (300 mg twice daily), lamivudine (150 mg twice daily), and efavirenz (600 mg once daily) or  
562 zidovudine (300 mg twice daily), lamivudine (150 mg twice daily), and efavirenz (600 mg once  
563 daily). The duration of double-blind treatment was at least 48 weeks. Study participants were:  
564 male (81%), Caucasian (51%), black (21%), and Hispanic (26%). The median age was 35 years,  
565 the median pretreatment CD4<sup>+</sup> cell count was 264 cells/mm<sup>3</sup>, and median plasma HIV-1 RNA  
566 was 4.79 log<sub>10</sub> copies/mL. The outcomes of randomized treatment are provided in Table 7.

567

568 **Table 7. Outcomes of Randomized Treatment Through Week 48 (CNA30024)**

Outcome	ZIAGEN plus Lamivudine plus Efavirenz (n = 324)	Zidovudine plus Lamivudine plus Efavirenz (n = 325)
Responder*	69% (73%)	69% (71%)
Virologic failures <sup>†</sup>	6%	4%
Discontinued due to adverse reactions	14%	16%
Discontinued due to other reasons <sup>‡</sup>	10%	11%

569 \* Patients achieved and maintained confirmed HIV-1 RNA  $\leq 50$  copies/mL ( $< 400$  copies/mL)  
570 through Week 48 (Roche AMPLICOR Ultrasensitive HIV-1 MONITOR<sup>®</sup> standard test 1.0  
571 PCR).

572 <sup>†</sup> Includes viral rebound, insufficient viral response according to the investigator, and failure to  
573 achieve confirmed  $\leq 50$  copies/mL by Week 48.

574 <sup>‡</sup> Includes consent withdrawn, lost to follow up, protocol violations, those with missing data,  
575 clinical progression, and other.

576

577 After 48 weeks of therapy, the median CD4+ cell count increases from baseline were  
578 209 cells/mm<sup>3</sup> in the group receiving ZIAGEN and 155 cells/mm<sup>3</sup> in the zidovudine group.  
579 Through Week 48, 8 subjects (2%) in the group receiving ZIAGEN (5 CDC classification C  
580 events and 3 deaths) and 5 subjects (2%) on the zidovudine arm (3 CDC classification C  
581 events and 2 deaths) experienced clinical disease progression.

582 CNA3005 was a multicenter, double-blind, controlled study in which  
583 562 HIV-1-infected, therapy-naïve adults were randomized to receive either ZIAGEN (300 mg  
584 twice daily) plus COMBIVIR (lamivudine 150 mg/zidovudine 300 mg twice daily), or indinavir  
585 (800 mg 3 times a day) plus COMBIVIR twice daily. The study was stratified at randomization  
586 by pre-entry plasma HIV-1 RNA 10,000 to 100,000 copies/mL and plasma HIV-1 RNA greater  
587 than 100,000 copies/mL. Study participants were male (87%), Caucasian (73%), black (15%),  
588 and Hispanic (9%). At baseline the median age was 36 years, the median baseline CD4+ cell  
589 count was 360 cells/mm<sup>3</sup>, and median baseline plasma HIV-1 RNA was 4.8 log<sub>10</sub> copies/mL.  
590 Proportions of patients with plasma HIV-1 RNA less than 400 copies/mL (using Roche  
591 AMPLICOR HIV-1 MONITOR Test) through 48 weeks of treatment are summarized in Table 8.  
592

593 **Table 8. Outcomes of Randomized Treatment Through Week 48 (CNA3005)**

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

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

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

596 <sup>‡</sup> Includes consent withdrawn, lost to follow up, protocol violations, those with missing data,  
597 clinical progression, and other.

598

599 Treatment response by plasma HIV-1 RNA strata is shown in Table 9.

600

601 **Table 9. Proportions of Responders Through Week 48 By Screening Plasma HIV-1 RNA**  
602 **Levels (CNA3005)**

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

603

604 In subjects with baseline viral load greater than 100,000 copies/mL, percentages of  
605 patients with HIV-1 RNA levels less than 50 copies/mL were 31% in the group receiving  
606 abacavir vs. 45% in the group receiving indinavir.

607 Through Week 48, an overall mean increase in CD4+ cell count of about 150 cells/mm<sup>3</sup>  
608 was observed in both treatment arms. Through Week 48, 9 subjects (3.4%) in the group receiving  
609 abacavir sulfate (6 CDC classification C events and 3 deaths) and 3 subjects (1.5%) in the group  
610 receiving indinavir (2 CDC classification C events and 1 death) experienced clinical disease  
611 progression.

612 CNA30021 was an international, multicenter, double-blind, controlled study in which  
613 770 HIV-1-infected, therapy-naive adults were randomized and received either abacavir 600 mg  
614 once daily or abacavir 300 mg twice daily, both in combination with lamivudine 300 mg once  
615 daily and efavirenz 600 mg once daily. The double-blind treatment duration was at least  
616 48 weeks. Study participants had a mean age of 37 years, were: male (81%), Caucasian (54%),  
617 black (27%), and American Hispanic (15%). The median baseline CD4+ cell count was  
618 262 cells/mm<sup>3</sup> (range 21 to 918 cells/mm<sup>3</sup>) and the median baseline plasma HIV-1 RNA was  
619 4.89 log<sub>10</sub> copies/mL (range: 2.60 to 6.99 log<sub>10</sub> copies/mL).

620 The outcomes of randomized treatment are provided in Table 10.

621

622 **Table 10. Outcomes of Randomized Treatment Through Week 48 (CNA30021)**

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

623 \* Patients achieved and maintained confirmed HIV-1 RNA <50 copies/mL (<400 copies/mL)  
624 through Week 48 (Roche AMPLICOR Ultrasensitive HIV-1 MONITOR standard test version  
625 1.0).

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

628 <sup>‡</sup> Includes consent withdrawn, lost to follow up, protocol violations, clinical progression, and  
629 other.

630

631 After 48 weeks of therapy, the median CD4+ cell count increases from baseline were  
632 188 cells/mm<sup>3</sup> in the group receiving abacavir 600 mg once daily and 200 cells/mm<sup>3</sup> in the group  
633 receiving abacavir 300 mg twice daily. Through Week 48, 6 subjects (2%) in the group receiving  
634 ZIAGEN 600 mg once daily (4 CDC classification C events and 2 deaths) and 10 subjects (3%)  
635 in the group receiving ZIAGEN 300 mg twice daily (7 CDC classification C events and 3 deaths)  
636 experienced clinical disease progression. None of the deaths were attributed to study  
637 medications.

## 638 **14.2 Pediatric Patients**

639 Therapy-Experienced Pediatric Patients: CNA3006 was a randomized, double-blind  
640 study comparing ZIAGEN 8 mg/kg twice daily plus lamivudine 4 mg/kg twice daily plus  
641 zidovudine 180 mg/m<sup>2</sup> twice daily versus lamivudine 4 mg/kg twice daily plus zidovudine  
642 180 mg/m<sup>2</sup> twice daily. Two hundred and five therapy-experienced pediatric patients were  
643 enrolled: female (56%), Caucasian (17%), black (50%), Hispanic (30%), median age of  
644 5.4 years, baseline CD4+ cell percent greater than 15% (median = 27%), and median baseline  
645 plasma HIV-1 RNA of 4.6 log<sub>10</sub> copies/mL. Eighty percent and 55% of patients had prior  
646 therapy with zidovudine and lamivudine, respectively, most often in combination. The median  
647 duration of prior nucleoside analogue therapy was 2 years. At 16 weeks the proportion of  
648 patients responding based on plasma HIV-1 RNA less than or equal to 400 copies/mL was  
649 significantly higher in patients receiving ZIAGEN plus lamivudine plus zidovudine compared  
650 with patients receiving lamivudine plus zidovudine, 13% versus 2%, respectively. Median  
651 plasma HIV-1 RNA changes from baseline were -0.53 log<sub>10</sub> copies/mL in the group receiving  
652 ZIAGEN plus lamivudine plus zidovudine compared with -0.21 log<sub>10</sub> copies/mL in the group  
653 receiving lamivudine plus zidovudine. Median CD4+ cell count increases from baseline were

654 69 cells/mm<sup>3</sup> in the group receiving ZIAGEN plus lamivudine plus zidovudine and 9 cells/mm<sup>3</sup>  
655 in the group receiving lamivudine plus zidovudine.

## 656 **15 REFERENCES**

657 1. Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study Group. *Lancet*.  
658 2008;371 (9622):1417-1426.

## 659 **16 HOW SUPPLIED/STORAGE AND HANDLING**

660 ZIAGEN Tablets, containing abacavir sulfate equivalent to 300 mg abacavir are yellow,  
661 biconvex, scored, capsule-shaped, film-coated, and imprinted with “GX 623” on both sides.  
662 They are packaged as follows:

663 Bottles of 60 tablets (NDC 0173-0661-01).

664 Unit dose blister packs of 60 tablets (NDC 0173-0661-00). Each pack contains 6 blister  
665 cards of 10 tablets each.

666 **Store at controlled room temperature of 20° to 25°C (68° to 77°F) (see USP).**

667 ZIAGEN Oral Solution is a clear to opalescent, yellowish, strawberry-banana-flavored  
668 liquid. Each mL of the solution contains abacavir sulfate equivalent to 20 mg of abacavir. It is  
669 packaged in plastic bottles as follows:

670 Bottles of 240 mL (NDC 0173-0664-00) with child-resistant closure. This product does  
671 not require reconstitution.

672 **Store at controlled room temperature of 20° to 25°C (68° to 77°F) (see USP). DO**  
673 **NOT FREEZE. May be refrigerated.**

## 674 **17 PATIENT COUNSELING INFORMATION**

675 See Medication Guide. (17.2)

### 676 **17.1 Information About Therapy With ZIAGEN**

677 Hypersensitivity Reaction: Inform patients:

- 678 • that a Medication Guide and Warning Card summarizing the symptoms of the abacavir  
679 hypersensitivity reaction and other product information will be dispensed by the pharmacist  
680 with each new prescription and refill of ZIAGEN, and encourage the patient to read the  
681 Medication Guide and Warning Card every time to obtain any new information that may be  
682 present about ZIAGEN. (The complete text of the Medication Guide is reprinted at the end of  
683 this document.)
- 684 • to carry the Warning Card with them.
- 685 • how to identify a hypersensitivity reaction [*see Medication Guide (17.2)*].
- 686 • that if they develop symptoms consistent with a hypersensitivity reaction they should call  
687 their doctor right away to determine if they should stop taking ZIAGEN.
- 688 • that a hypersensitivity reaction can worsen and lead to hospitalization or death if ZIAGEN is  
689 not immediately discontinued.
- 690 • that in one study, more severe hypersensitivity reactions were seen when ZIAGEN was dosed  
691 600 mg once daily.

- 692 • to not restart ZIAGEN or any other abacavir-containing product following a hypersensitivity  
693 reaction because more severe symptoms can occur within hours and may include  
694 life-threatening hypotension and death.
  - 695 • that a hypersensitivity reaction is usually reversible if it is detected promptly and ZIAGEN is  
696 stopped right away.
  - 697 • that if they have interrupted ZIAGEN for reasons other than symptoms of hypersensitivity  
698 (for example, those who have an interruption in drug supply), a serious or fatal  
699 hypersensitivity reaction may occur with reintroduction of abacavir.
  - 700 • to not restart ZIAGEN or any other abacavir-containing product without medical consultation  
701 and that restarting abacavir needs to be undertaken only if medical care can be readily  
702 accessed by the patient or others.
  - 703 • ZIAGEN should not be coadministered with EPZICOM<sup>®</sup> or TRIZIVIR<sup>®</sup>.
- 704 Lactic Acidosis/Hepatomegaly: Inform patients that some HIV medicines, including  
705 ZIAGEN, can cause a rare, but serious condition called lactic acidosis with liver enlargement  
706 (hepatomegaly).
- 707 Redistribution/Accumulation of Body Fat: Inform patients that redistribution or  
708 accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause  
709 and long-term health effects of these conditions are not known at this time.
- 710 Information About HIV-1 Infection: ZIAGEN is not a cure for HIV-1 infection and  
711 patients may continue to experience illnesses associated with HIV-1 infection, including  
712 opportunistic infections. Patients should remain under the care of a physician when using  
713 ZIAGEN. Advise patients that the use of ZIAGEN has not been shown to reduce the risk of  
714 transmission of HIV-1 to others through sexual contact or blood contamination. Patients should  
715 be informed to take all HIV medications exactly as prescribed.

716

## 717 **17.2 FDA Approved Patient Labeling**

718

### **MEDICATION GUIDE**

719

720

#### **ZIAGEN<sup>®</sup> (ZY-uh-jen) Tablets**

721

#### **ZIAGEN<sup>®</sup> Oral Solution**

722

**Generic name:** abacavir (uh-BACK-ah-veer) sulfate tablets and oral solution

723

724

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

728

729

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

- 730 • **Serious Allergic Reaction to Abacavir.** ZIAGEN contains abacavir (also contained in  
731 EPZICOM<sup>®</sup> and TRIZIVIR<sup>®</sup>). Patients taking ZIAGEN may have a serious allergic reaction  
732 (hypersensitivity reaction) that can cause death. **Your risk of this allergic reaction is much**  
733 **higher if you have a gene variation called HLA-B\*5701 than if you do not. Your doctor**  
734 **can determine with a blood test if you have this gene variation. If you get a symptom**  
735 **from 2 or more of the following groups while taking ZIAGEN, call your doctor right**  
736 **away to determine if you should stop taking this medicine.**  
737

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

738

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

741

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

747

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

753

- 754 • **Lactic Acidosis.** Some human immunodeficiency virus (HIV-1) medicines, including  
755 **ZIAGEN, can cause a rare but serious condition called lactic acidosis with liver**  
756 **enlargement (hepatomegaly).** Nausea and tiredness that don't get better may be symptoms  
757 of lactic acidosis. In some cases this condition can cause death. Women, overweight people,  
758 and people who have taken HIV-1 medicines like ZIAGEN for a long time have a higher  
759 chance of getting lactic acidosis and liver enlargement. Lactic acidosis is a medical  
760 emergency and must be treated in the hospital.

761

762 ZIAGEN can have other serious side effects. Be sure to read the section below entitled "What are  
763 the possible side effects of ZIAGEN?"

764

765 **What is ZIAGEN?**

766 ZIAGEN is a prescription medicine used to treat HIV-1 infection. ZIAGEN is taken by mouth as  
767 a tablet or a strawberry-banana-flavored liquid. ZIAGEN is a medicine called a nucleoside  
768 analogue reverse transcriptase inhibitor (NRTI). ZIAGEN is always used with other anti-HIV-1  
769 medicines. When used in combination with these other medicines, ZIAGEN helps lower the  
770 amount of HIV-1 found in your blood. This helps to keep your immune system as healthy as  
771 possible so that it can help fight infection.

772

773 Different combinations of medicines are used to treat HIV-1 infection. You and your doctor  
774 should discuss which combination of medicines is best for you.

775

- 776 • **ZIAGEN does not cure HIV-1 infection or AIDS.** We do not know if ZIAGEN will help  
777 you live longer or have fewer of the medical problems that people get with HIV-1 or AIDS.  
778 It is very important that you see your doctor regularly while you are taking ZIAGEN.
- 779 • **ZIAGEN does not lower the risk of passing HIV-1 to other people through sexual  
780 contact, sharing needles, or being exposed to your blood.** For your health and the health of  
781 others, it is important to always practice safe sex by using a latex or polyurethane condom or  
782 other barrier method to lower the chance of sexual contact with semen, vaginal secretions, or  
783 blood. Never use or share dirty needles.

784

785 ZIAGEN has not been studied in children under 3 months of age or in adults over 65 years of  
786 age.

787

788 **Who should not take ZIAGEN?**

789 **Do not take ZIAGEN if you:**

- 790 • **have ever had a serious allergic reaction (a hypersensitivity reaction) to ZIAGEN or  
791 any other medicine that has abacavir as one of its ingredients (EPZICOM and  
792 TRIZIVIR).** See the end of this Medication Guide for a complete list of ingredients in  
793 ZIAGEN.
- 794 • **have a liver that does not function properly.**

795

796 **Before starting ZIAGEN, tell your doctor about all of your medical conditions, including if  
797 you:**

- 798 • **have been tested and know whether or not you have a particular gene variation called  
799 HLA-B\*5701.**
- 800 • **are pregnant or planning to become pregnant.** We do not know if ZIAGEN will harm  
801 your unborn child. You and your doctor will need to decide if ZIAGEN is right for you. If  
802 you use ZIAGEN while you are pregnant, talk to your doctor about how you can be on the  
803 Antiviral Pregnancy Registry for ZIAGEN.

- 804 • **are breastfeeding.** We do not know if ZIAGEN can be passed to your baby in your breast  
805 milk and whether it could harm your baby. Also, mothers with HIV-1 should not breastfeed  
806 because HIV-1 can be passed to the baby in the breast milk.
- 807 • **have liver problems.**
- 808 • **have heart problems, smoke, or suffer from diseases that increase your risk of heart**  
809 **disease such as high blood pressure, high cholesterol, or diabetes.**

810

811 **Tell your doctor about all the medicines you take, including prescription and**  
812 **nonprescription medicines, vitamins, and herbal supplements. Especially tell your doctor if**  
813 **you take:**

- 814 • **methadone**
- 815 • **EPZICOM (abacavir sulfate and lamivudine) and TRIZIVIR (abacavir sulfate,**  
816 **lamivudine, and zidovudine).**

817

### 818 **How should I take ZIAGEN?**

- 819 • **Take ZIAGEN by mouth exactly as your doctor prescribes it.** Your doctor will tell you  
820 the right dose to take. The usual doses are 1 tablet twice a day or 2 tablets once a day. Do not  
821 skip doses.
- 822 • **Children aged 3 months and older can also take ZIAGEN.** The child's healthcare professional  
823 will decide the right dose and formulation based on the child's weight. The dose should not  
824 exceed the recommended adult dose.
- 825 • **You can take ZIAGEN with or without food.**
- 826 • **If you miss a dose of ZIAGEN, take the missed dose right away. Then, take the next**  
827 **dose at the usual time.**
- 828 • **Do not let your ZIAGEN run out.**
- 829 • **Starting ZIAGEN again can cause a serious allergic or life-threatening reaction, even if**  
830 **you never had an allergic reaction to it before.** If you run out of ZIAGEN even for a few  
831 days, you must ask your doctor if you can start ZIAGEN again. If your doctor tells you that  
832 you can take ZIAGEN again, start taking it when you are around medical help or people who  
833 can call a doctor if you need one.
- 834 • **If you stop your anti-HIV drugs, even for a short time, the amount of virus in your**  
835 **blood may increase and the virus may become harder to treat.**
- 836 • **If you take too much ZIAGEN, call your doctor or poison control center right away.**

837

### 838 **What should I avoid while taking ZIAGEN?**

- 839 • **Do not take EPZICOM (abacavir sulfate and lamivudine) or TRIZIVIR (abacavir sulfate,**  
840 **lamivudine, and zidovudine) while taking ZIAGEN.** Some of these medicines are already in  
841 ZIAGEN.

842

843 **Avoid doing things that can spread HIV-1 infection**, as ZIAGEN does not stop you from  
844 passing the HIV-1 infection to others.

- 845 • **Do not share needles or other injection equipment.**
- 846 • **Do not share personal items that can have blood or body fluids on them, like**  
847 **toothbrushes and razor blades.**
- 848 • **Do not have any kind of sex without protection.** Always practice safe sex by using a latex  
849 or polyurethane condom or other barrier method to lower the chance of sexual contact with  
850 semen, vaginal secretions, or blood.
- 851 • **Do not breastfeed.** We do not know if ZIAGEN can be passed to your baby in your breast  
852 milk and whether it could harm your baby. Also, mothers with HIV-1 should not breastfeed  
853 because HIV-1 can be passed to the baby in the breast milk.

854

### 855 **What are the possible side effects of ZIAGEN?**

856 **ZIAGEN can cause the following serious side effects:**

- 857 • **Serious allergic reaction that can cause death.** (See "What is the most important  
858 information I should know about ZIAGEN?" at the beginning of this Medication Guide.)
- 859 • **Lactic acidosis with liver enlargement (hepatomegaly) that can cause death.** (See "What  
860 is the most important information I should know about ZIAGEN?" at the beginning of this  
861 Medication Guide.)
- 862 • **Changes in immune system.** When you start taking HIV medicines, your immune system  
863 may get stronger and could begin to fight infections that have been hidden in your body, such  
864 as pneumonia, herpes virus, or tuberculosis. If you have new symptoms after starting your  
865 HIV medicines, be sure to tell your doctor.
- 866 • **Changes in body fat.** These changes have happened in patients taking antiretroviral  
867 medicines like ZIAGEN. The changes may include an increased amount of fat in the upper  
868 back and neck ("buffalo hump"), breast, and around the back, chest, and stomach area. Loss  
869 of fat from the legs, arms, and face may also happen. The cause and long-term health effects  
870 of these conditions are not known.

871

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

875

876 The most common side effects of ZIAGEN include nausea, vomiting, tiredness, headache,  
877 diarrhea, trouble sleeping, fever and chills, and loss of appetite. Most of these side effects did not  
878 cause people to stop taking ZIAGEN.

879

880 This list of side effects is not complete. Call your doctor for medical advice about side effects.

881 You may report side effects to FDA at 1-800-FDA-1088.

882

883 **How should I store ZIAGEN?**

- 884 • Store ZIAGEN at room temperature, between 68° to 77°F (20° to 25°C). Do not freeze  
885 ZIAGEN.  
886 • **Keep ZIAGEN and all medicines out of the reach of children.**  
887

888 **General information for safe and effective use of ZIAGEN**

889 Medicines are sometimes prescribed for conditions that are not mentioned in Medication Guides.  
890 Do not use ZIAGEN for a condition for which it was not prescribed. Do not give ZIAGEN to  
891 other people, even if they have the same symptoms that you have. It may harm them.  
892

893 This Medication Guide summarizes the most important information about ZIAGEN. If you  
894 would like more information, talk with your doctor. You can ask your doctor or pharmacist for  
895 the information that is written for healthcare professionals or call 1-888-825-5249.  
896

897 **What are the ingredients in ZIAGEN?**

898 **Tablets:** Each tablet contains abacavir sulfate equivalent to 300 mg of abacavir as active  
899 ingredient and the following inactive ingredients: colloidal silicon dioxide, magnesium stearate,  
900 microcrystalline cellulose, and sodium starch glycolate. The film-coating is made of  
901 hypromellose, polysorbate 80, synthetic yellow iron oxide, titanium dioxide, and triacetin.

902 **Oral Solution:** Each milliliter (1 mL) of ZIAGEN Oral Solution contains abacavir sulfate  
903 equivalent to 20 mg of abacavir (i.e., 20 mg/mL) as active ingredient and the following inactive  
904 ingredients: artificial strawberry and banana flavors, citric acid (anhydrous), methylparaben and  
905 propylparaben (added as preservatives), propylene glycol, saccharin sodium, sodium citrate  
906 (dihydrate), sorbitol solution, and water.  
907

908 *This Medication Guide has been approved by the US Food and Drug Administration.*  
909  
910



911  
912 GlaxoSmithKline  
913 Research Triangle Park, NC 27709  
914

915 ©2008, GlaxoSmithKline. All rights reserved.  
916

917 Month 200x  
918 ZGN:xMG