

## 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, for oral use  
ZIAGEN (abacavir sulfate) 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

Warnings and Precautions, Immune Reconstitution Syndrome (5.3) ----- 11/2011

### 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  $\geq 10\%$ ) 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  $\geq 5\%$ ) 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 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. (7.1)
- Methadone: An increased methadone dose may be required in a small number of patients. (7.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 03/2012

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1 **FULL PRESCRIBING INFORMATION**

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

4 **Hypersensitivity Reactions:** Serious and sometimes fatal hypersensitivity reactions have  
5 been associated with ZIAGEN<sup>®</sup> (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:** Lactic acidosis and severe hepatomegaly  
30 with steatosis, including fatal cases, have been reported with the use of nucleoside  
31 analogues alone or in combination, including ZIAGEN and other antiretrovirals [*see*  
32 *Warnings and Precautions (5.2)*].

33 **1 INDICATIONS AND USAGE**

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

36 Additional important information on the use of ZIAGEN for treatment of HIV-1  
37 infection:  
38 ZIAGEN is one of multiple products containing abacavir. Before starting ZIAGEN, review  
39 medical history for prior exposure to any abacavir-containing product in order to avoid  
40 reintroduction in a patient with a history of hypersensitivity to abacavir [see Warnings and  
41 Precautions (5.1), Adverse Reactions (6)].

## 42 **2 DOSAGE AND ADMINISTRATION**

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

### 49 **2.1 Adult Patients**

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

### 52 **2.2 Pediatric Patients**

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

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

62  
63 **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

### 64 **2.3 Patients With Hepatic Impairment**

65 The recommended dose of ZIAGEN in patients with mild hepatic impairment  
66 (Child-Pugh score 5 to 6) is 200 mg twice daily. To enable dose reduction, ZIAGEN Oral  
67 Solution (10 mL twice daily) should be used for the treatment of these patients. The safety,  
68

69 efficacy, and pharmacokinetic properties of abacavir have not been established in patients with  
70 moderate to severe hepatic impairment; therefore, ZIAGEN is contraindicated in these patients.

### 71 **3 DOSAGE FORMS AND STRENGTHS**

72 ZIAGEN Tablets contain 300 mg of abacavir as abacavir sulfate. The tablets are yellow,  
73 biconvex, scored, capsule-shaped, film-coated, and imprinted with “GX 623” on both sides.

74 ZIAGEN Oral Solution contains 20 mg/mL of abacavir as abacavir sulfate. The solution  
75 is a clear to opalescent, yellowish, strawberry-banana-flavored liquid.

### 76 **4 CONTRAINDICATIONS**

77 ZIAGEN is contraindicated in patients with:

- 78 • previously demonstrated hypersensitivity to abacavir or any other component of the  
79 products. NEVER restart ZIAGEN or any other abacavir-containing product following a  
80 hypersensitivity reaction to abacavir, regardless of HLA-B\*5701 status [*see Warnings and*  
81 *Precautions (5.1), Adverse Reactions (6)*].
- 82 • moderate or severe hepatic impairment [*see Dosage and Administration (2.3)*].

### 83 **5 WARNINGS AND PRECAUTIONS**

#### 84 **5.1 Hypersensitivity Reaction**

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

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

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

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

103 Group 1: Fever

104 Group 2: Rash

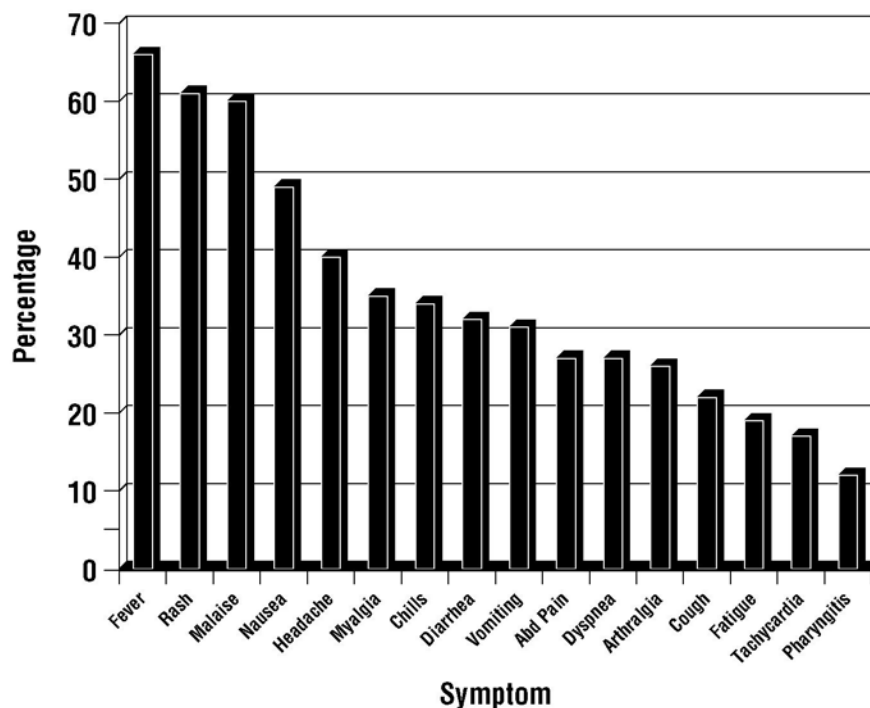
105 Group 3: Gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain)

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

107 Group 5: Respiratory (including dyspnea, cough, or pharyngitis).  
108 Hypersensitivity to abacavir following the presentation of a single sign or symptom has  
109 been reported infrequently.

110 Hypersensitivity to abacavir was reported in approximately 8% of 2,670 patients  
111 (n = 206) in 9 clinical trials (range: 2% to 9%) with enrollment from November 1999 to February  
112 2002. Data on time to onset and symptoms of suspected hypersensitivity were collected on a  
113 detailed data collection module. The frequencies of symptoms are shown in Figure 1. Symptoms  
114 usually appeared within the first 6 weeks of treatment with abacavir, although the reaction may  
115 occur at any time during therapy. Median time to onset was 9 days; 89% appeared within the first  
116 6 weeks; 95% of patients reported symptoms from 2 or more of the 5 groups listed above.

117  
118 **Figure 1. Hypersensitivity-Related Symptoms Reported With**  
119 **≥10% Frequency in Clinical Trials (n = 206 Patients)**



120  
121  
122 Other less common signs and symptoms of hypersensitivity include lethargy, myolysis,  
123 edema, abnormal chest x-ray findings (predominantly infiltrates, which can be localized), and  
124 paresthesia. Anaphylaxis, liver failure, renal failure, hypotension, adult respiratory distress  
125 syndrome, respiratory failure, and death have occurred in association with hypersensitivity  
126 reactions. In one study, 4 patients (11%) receiving ZIAGEN 600 mg once daily experienced  
127 hypotension with a hypersensitivity reaction compared with 0 patients receiving ZIAGEN  
128 300 mg twice daily.

129 Physical findings associated with hypersensitivity to abacavir in some patients include  
130 lymphadenopathy, mucous membrane lesions (conjunctivitis and mouth ulcerations), and rash.

131 The rash usually appears maculopapular or urticarial, but may be variable in appearance. There  
132 have been reports of erythema multiforme. Hypersensitivity reactions have occurred without  
133 rash.

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

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

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

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

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

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

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

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

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

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

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

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

## 186 **5.2 Lactic Acidosis/Severe Hepatomegaly With Steatosis**

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

## 196 **5.3 Immune Reconstitution Syndrome**

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

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

## 206 **5.4 Fat Redistribution**

207 Redistribution/accumulation of body fat including central obesity, dorsocervical fat  
208 enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and  
209 "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The

210 mechanism and long-term consequences of these events are currently unknown. A causal  
211 relationship has not been established.

## 212 **5.5 Myocardial Infarction**

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

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

## 223 **6 ADVERSE REACTIONS**

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

- 226 • Serious and sometimes fatal hypersensitivity reaction. In one study, once-daily dosing of  
227 abacavir was associated with more severe hypersensitivity reactions [*see Boxed Warning,*  
228 *Warnings and Precautions (5.1)*].
- 229 • Lactic acidosis and severe hepatomegaly [*see Boxed Warning, Warnings and Precautions*  
230 *(5.2)*].
- 231 • Immune reconstitution syndrome [*see Warnings and Precautions (5.3)*].
- 232 • Fat redistribution [*see Warnings and Precautions (5.4)*].
- 233 • Myocardial infarction [*see Warnings and Precautions (5.5)*].

### 234 **6.1 Clinical Trials Experience**

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

238 Adults: Therapy-Naive Adults: Treatment-emergent clinical adverse reactions (rated by  
239 the investigator as moderate or severe) with a greater than or equal to 5% frequency during  
240 therapy with ZIAGEN 300 mg twice daily, lamivudine 150 mg twice daily, and efavirenz  
241 600 mg daily compared with zidovudine 300 mg twice daily, lamivudine 150 mg twice daily,  
242 and efavirenz 600 mg daily from CNA30024 are listed in Table 2.

243



244 **Table 2. Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate**  
 245 **Intensity (Grades 2-4, ≥5% Frequency) in Therapy-Naive Adults (CNA30024<sup>a</sup>) Through**  
 246 **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>b</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%

247 <sup>a</sup> This study used double-blind ascertainment of suspected hypersensitivity reactions. During  
 248 the blinded portion of the study, suspected hypersensitivity to abacavir was reported by  
 249 investigators in 9% of 324 patients in the abacavir group and 3% of 325 patients in the  
 250 zidovudine group.

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

253  
 254 Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or  
 255 severe) with a greater than or equal to 5% frequency during therapy with ZIAGEN 300 mg twice  
 256 daily, lamivudine 150 mg twice daily, and zidovudine 300 mg twice daily compared with  
 257 indinavir 800 mg 3 times daily, lamivudine 150 mg twice daily, and zidovudine 300 mg twice  
 258 daily from CNA3005 are listed in Table 3.

259

260 **Table 3. Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate**  
 261 **Intensity (Grades 2-4, ≥5% Frequency) in Therapy-Naive Adults (CNA3005) Through**  
 262 **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%

263  
 264 Five patients receiving ZIAGEN in CNA3005 experienced worsening of pre-existing  
 265 depression compared with none in the indinavir arm. The background rates of pre-existing  
 266 depression were similar in the 2 treatment arms.

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

268 Treatment-emergent clinical adverse reactions (rated by the investigator as at least moderate)  
 269 with a greater than or equal to 5% frequency during therapy with ZIAGEN 600 mg once daily or  
 270 ZIAGEN 300 mg twice daily both in combination with lamivudine 300 mg once daily and  
 271 efavirenz 600 mg once daily from CNA30021 were similar. For hypersensitivity reactions,  
 272 patients receiving ZIAGEN once daily showed a rate of 9% in comparison with a rate of 7% for  
 273 patients receiving ZIAGEN twice daily. However, patients receiving ZIAGEN 600 mg once  
 274 daily, experienced a significantly higher incidence of severe drug hypersensitivity reactions and  
 275 severe diarrhea compared with patients who received ZIAGEN 300 mg twice daily. Five percent  
 276 (5%) of patients receiving ZIAGEN 600 mg once daily had severe drug hypersensitivity  
 277 reactions compared with 2% of patients receiving ZIAGEN 300 mg twice daily. Two percent  
 278 (2%) of patients receiving ZIAGEN 600 mg once daily had severe diarrhea while none of the  
 279 patients receiving ZIAGEN 300 mg twice daily had this event.

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

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

284

285 **Table 4. Laboratory Abnormalities (Grades 3-4) in Therapy-Naive Adults (CNA30024)**  
 286 **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%

287 ULN = Upper limit of normal.

288 n = Number of patients assessed.

289

290 Laboratory abnormalities in CNA3005 are listed in Table 5.

291

292 **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%)

293 ULN = Upper limit of normal.

294 n = Number of patients assessed.

295

296 The frequencies of treatment-emergent laboratory abnormalities were comparable  
297 between treatment groups in CNA30021.

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

303

304 **Table 6. Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate**  
305 **Intensity (Grades 2-4, ≥5% Frequency) in Therapy-Experienced Pediatric Patients**  
306 **(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%

307

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

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

## 316 **6.2 Postmarketing Experience**

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

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

323 Cardiovascular: Myocardial infarction.

324 Hepatic: Lactic acidosis and hepatic steatosis.

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

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

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

## 332 **7 DRUG INTERACTIONS**

### 333 **7.1 Ethanol**

334 Abacavir has no effect on the pharmacokinetic properties of ethanol. Ethanol decreases  
335 the elimination of abacavir causing an increase in overall exposure [*see Clinical Pharmacology*  
336 (*12.3*)].

### 337 **7.2 Methadone**

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

## 344 **8 USE IN SPECIFIC POPULATIONS**

### 345 **8.1 Pregnancy**

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

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

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

### 360 **8.3 Nursing Mothers**

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

363 Although it is not known if abacavir is excreted in human milk, abacavir is secreted into  
364 the milk of lactating rats. Because of both the potential for HIV-1 transmission and the potential

365 for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if  
366 they are receiving ZIAGEN.

#### 367 **8.4 Pediatric Use**

368 The safety and effectiveness of ZIAGEN have been established in pediatric patients  
369 3 months to 13 years of age. Use of ZIAGEN in these age groups is supported by  
370 pharmacokinetic studies and evidence from adequate and well-controlled studies of ZIAGEN in  
371 adults and pediatric patients [see *Dosage and Administration (2.2)*, *Clinical Pharmacology*  
372 *(12.3)*, *Clinical Studies (14.2)*].

#### 373 **8.5 Geriatric Use**

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

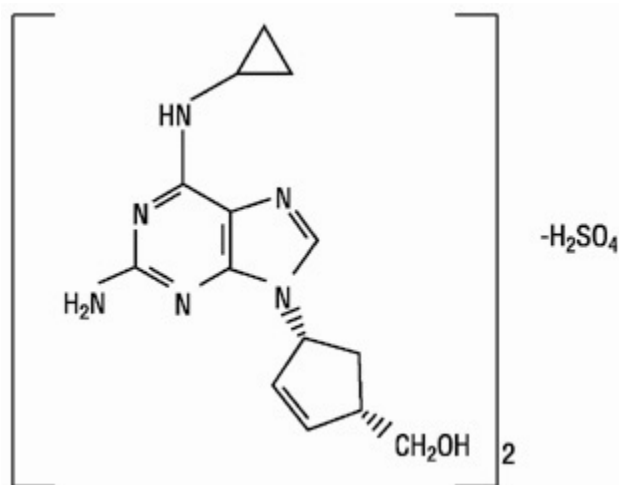
### 378 **10 OVERDOSAGE**

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

### 381 **11 DESCRIPTION**

382 ZIAGEN is the brand name for abacavir sulfate, a synthetic carbocyclic nucleoside  
383 analogue with inhibitory activity against HIV-1. The chemical name of abacavir sulfate is  
384 (1*S*,*cis*)-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate  
385 (salt) (2:1). Abacavir sulfate is the enantiomer with 1*S*, 4*R* absolute configuration on the  
386 cyclopentene ring. It has a molecular formula of  $(C_{14}H_{18}N_6O)_2 \cdot H_2SO_4$  and a molecular weight  
387 of 670.76 daltons. It has the following structural formula:

388



389

390

391 Abacavir sulfate is a white to off-white solid with a solubility of approximately  
392 77 mg/mL in distilled water at 25°C. It has an octanol/water (pH 7.1 to 7.3) partition coefficient  
393 (log *P*) of approximately 1.20 at 25°C.

394 ZIAGEN Tablets are for oral administration. Each tablet contains abacavir sulfate  
395 equivalent to 300 mg of abacavir as active ingredient and the following inactive ingredients:  
396 colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, and sodium starch  
397 glycolate. The tablets are coated with a film that is made of hypromellose, polysorbate 80,  
398 synthetic yellow iron oxide, titanium dioxide, and triacetin.

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

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

## 406 **12 CLINICAL PHARMACOLOGY**

### 407 **12.1 Mechanism of Action**

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

### 409 **12.3 Pharmacokinetics**

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

414 *Absorption and Bioavailability:* Abacavir was rapidly and extensively absorbed after  
415 oral administration. The geometric mean absolute bioavailability of the tablet was 83%. After  
416 oral administration of 300 mg twice daily in 20 patients, the steady-state peak serum abacavir  
417 concentration ( $C_{max}$ ) was  $3.0 \pm 0.89$  mcg/mL (mean  $\pm$  SD) and  $AUC_{(0-12\text{ hr})}$  was  
418  $6.02 \pm 1.73$  mcg•hr/mL. After oral administration of a single dose of 600 mg of abacavir in  
419 20 patients,  $C_{max}$  was  $4.26 \pm 1.19$  mcg/mL (mean  $\pm$  SD) and  $AUC_{\infty}$  was  
420  $11.95 \pm 2.51$  mcg•hr/mL.

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

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

428 *Metabolism:* In humans, abacavir is not significantly metabolized by cytochrome  
429 P450 enzymes. The primary routes of elimination of abacavir are metabolism by alcohol

430 dehydrogenase (to form the 5'-carboxylic acid) and glucuronyl transferase (to form the  
431 5'-glucuronide). The metabolites do not have antiviral activity. In vitro experiments reveal that  
432 abacavir does not inhibit human CYP3A4, CYP2D6, or CYP2C9 activity at clinically relevant  
433 concentrations.

434 **Elimination:** Elimination of abacavir was quantified in a mass balance study following  
435 administration of a 600-mg dose of <sup>14</sup>C-abacavir: 99% of the radioactivity was recovered, 1.2%  
436 was excreted in the urine as abacavir, 30% as the 5'-carboxylic acid metabolite, 36% as the  
437 5'-glucuronide metabolite, and 15% as unidentified minor metabolites in the urine. Fecal  
438 elimination accounted for 16% of the dose.

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

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

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

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

458 **Pediatric Patients:** The pharmacokinetics of abacavir have been studied after either  
459 single or repeat doses of ZIAGEN in 68 pediatric patients. Following multiple-dose  
460 administration of ZIAGEN 8 mg/kg twice daily, steady-state  $AUC_{(0-12 \text{ hr})}$  and  $C_{\max}$  were  
461  $9.8 \pm 4.56$  mcg•hr/mL and  $3.71 \pm 1.36$  mcg/mL (mean  $\pm$  SD), respectively [see Use in Specific  
462 Populations (8.4)]. In addition, to support dosing of ZIAGEN scored tablet (300 mg) for  
463 pediatric patients 14 to greater than 30 kg, analysis of actual and simulated pharmacokinetic data  
464 indicated comparable exposures are expected following administration of 300 mg scored tablet  
465 and the 8 mg/kg dosing regimen using oral solution.

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



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

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

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

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

484 *Ethanol:* Due to their common metabolic pathways via alcohol dehydrogenase, the  
485 pharmacokinetic interaction between abacavir and ethanol was studied in 24 HIV-1-infected  
486 male patients. Each patient received the following treatments on separate occasions: a single  
487 600-mg dose of abacavir, 0.7 g/kg ethanol (equivalent to 5 alcoholic drinks), and abacavir  
488 600 mg plus 0.7 g/kg ethanol. Coadministration of ethanol and abacavir resulted in a 41%  
489 increase in abacavir AUC<sub>∞</sub> and a 26% increase in abacavir t<sub>1/2</sub>. In males, abacavir had no effect  
490 on the pharmacokinetic properties of ethanol, so no clinically significant interaction is expected  
491 in men. This interaction has not been studied in females.

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

#### 499 **12.4 Microbiology**

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

508 **Antiviral Activity:** The antiviral activity of abacavir against HIV-1 was evaluated against  
509 a T-cell tropic laboratory strain HIV-1<sub>III<sub>B</sub></sub> in lymphoblastic cell lines, a monocyte/macrophage  
510 tropic laboratory strain HIV-1<sub>BaL</sub> in primary monocytes/macrophages, and clinical isolates in  
511 peripheral blood mononuclear cells. The concentration of drug necessary to effect viral  
512 replication by 50 percent (EC<sub>50</sub>) ranged from 3.7 to 5.8 μM (1 μM = 0.28 mcg/mL) and 0.07 to  
513 1.0 μM against HIV-1<sub>III<sub>B</sub></sub> and HIV-1<sub>BaL</sub>, respectively, and was 0.26 ± 0.18 μM against 8 clinical  
514 isolates. The EC<sub>50</sub> values of abacavir against different HIV-1 clades (A-G) ranged from 0.0015  
515 to 1.05 μM, and against HIV-2 isolates, from 0.024 to 0.49 μM. Abacavir had synergistic  
516 activity in cell culture in combination with the nucleoside reverse transcriptase inhibitor (NRTI)  
517 zidovudine, the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, and the  
518 protease inhibitor (PI) amprenavir; and additive activity in combination with the NRTIs  
519 didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine. Ribavirin (50 μM)  
520 had no effect on the anti-HIV-1 activity of abacavir in cell culture.

521 **Resistance:** HIV-1 isolates with reduced susceptibility to abacavir have been selected in  
522 cell culture and were also obtained from patients treated with abacavir. Genotypic analysis of  
523 isolates selected in cell culture and recovered from abacavir-treated patients demonstrated that  
524 amino acid substitutions K65R, L74V, Y115F, and M184V/I in RT contributed to abacavir  
525 resistance. In a study of therapy-naïve adults receiving ZIAGEN 600 mg once daily (n = 384) or  
526 300 mg twice daily (n = 386), in a background regimen of lamivudine 300 mg once daily and  
527 efavirenz 600 mg once daily (CNA30021), the incidence of virologic failure at 48 weeks was  
528 similar between the 2 groups (11% in both arms). Genotypic (n = 38) and phenotypic analyses  
529 (n = 35) of virologic failure isolates from this study showed that the RT substitutions that  
530 emerged during abacavir once-daily and twice-daily therapy were K65R, L74V, Y115F, and  
531 M184V/I. The substitution M184V/I was the most commonly observed substitution in virologic  
532 failure isolates from patients receiving abacavir once daily (56%, 10/18) and twice daily (40%,  
533 8/20).

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

538 **Cross-Resistance:** Cross-resistance has been observed among NRTIs. Isolates  
539 containing abacavir resistance-associated substitutions, namely, K65R, L74V, Y115F, and  
540 M184V, exhibited cross-resistance to didanosine, emtricitabine, lamivudine, tenofovir, and  
541 zalcitabine in cell culture and in patients. The K65R substitution can confer resistance to  
542 abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine; the L74V  
543 substitution can confer resistance to abacavir, didanosine, and zalcitabine; and the M184V  
544 substitution can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, and  
545 zalcitabine. An increasing number of thymidine analogue mutations (TAMs: M41L, D67N,  
546 K70R, L210W, T215Y/F, K219E/R/H/Q/N) is associated with a progressive reduction in  
547 abacavir susceptibility.

548 **13 NONCLINICAL TOXICOLOGY**

549 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

550 Carcinogenicity: Abacavir was administered orally at 3 dosage levels to separate groups  
551 of mice and rats in 2-year carcinogenicity studies. Results showed an increase in the incidence of  
552 malignant and non-malignant tumors. Malignant tumors occurred in the preputial gland of males  
553 and the clitoral gland of females of both species, and in the liver of female rats. In addition,  
554 non-malignant tumors also occurred in the liver and thyroid gland of female rats. These  
555 observations were made at systemic exposures in the range of 6 to 32 times the human exposure  
556 at the recommended dose. It is not known how predictive the results of rodent carcinogenicity  
557 studies may be for humans.

558 Mutagenicity: Abacavir induced chromosomal aberrations both in the presence and  
559 absence of metabolic activation in an in vitro cytogenetic study in human lymphocytes. Abacavir  
560 was mutagenic in the absence of metabolic activation, although it was not mutagenic in the  
561 presence of metabolic activation in an L5178Y mouse lymphoma assay. Abacavir was  
562 clastogenic in males and not clastogenic in females in an in vivo mouse bone marrow  
563 micronucleus assay.

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

566 Impairment of Fertility: Abacavir had no adverse effects on the mating performance or  
567 fertility of male and female rats at a dose approximately 8 times the human exposure at the  
568 recommended dose based on body surface area comparisons.

569 **13.2 Animal Toxicology and/or Pharmacology**

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

573 **14 CLINICAL STUDIES**

574 **14.1 Adults**

575 Therapy-Naive Adults: CNA30024 was a multicenter, double-blind, controlled study in  
576 which 649 HIV-1-infected, therapy-naive adults were randomized and received either ZIAGEN  
577 (300 mg twice daily), lamivudine (150 mg twice daily), and efavirenz (600 mg once daily) or  
578 zidovudine (300 mg twice daily), lamivudine (150 mg twice daily), and efavirenz (600 mg once  
579 daily). The duration of double-blind treatment was at least 48 weeks. Study participants were:  
580 male (81%), Caucasian (51%), black (21%), and Hispanic (26%). The median age was 35 years,  
581 the median pretreatment CD4+ cell count was 264 cells/mm<sup>3</sup>, and median plasma HIV-1 RNA  
582 was 4.79 log<sub>10</sub> copies/mL. The outcomes of randomized treatment are provided in Table 7.

583

584 **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 <sup>a</sup>	69% (73%)	69% (71%)
Virologic failures <sup>b</sup>	6%	4%
Discontinued due to adverse reactions	14%	16%
Discontinued due to other reasons <sup>c</sup>	10%	11%

585 <sup>a</sup> Patients achieved and maintained confirmed HIV-1 RNA ≤50 copies/mL (<400 copies/mL)  
 586 through Week 48 (Roche AMPLICOR Ultrasensitive HIV-1 MONITOR<sup>®</sup> standard test 1.0  
 587 PCR).

588 <sup>b</sup> Includes viral rebound, insufficient viral response according to the investigator, and failure to  
 589 achieve confirmed ≤50 copies/mL by Week 48.

590 <sup>c</sup> Includes consent withdrawn, lost to follow up, protocol violations, those with missing data,  
 591 clinical progression, and other.

592

593 After 48 weeks of therapy, the median CD4+ cell count increases from baseline were  
 594 209 cells/mm<sup>3</sup> in the group receiving ZIAGEN and 155 cells/mm<sup>3</sup> in the zidovudine group.  
 595 Through Week 48, 8 subjects (2%) in the group receiving ZIAGEN (5 CDC classification C  
 596 events and 3 deaths) and 5 subjects (2%) on the zidovudine arm (3 CDC classification C  
 597 events and 2 deaths) experienced clinical disease progression.

598 CNA3005 was a multicenter, double-blind, controlled study in which  
 599 562 HIV-1-infected, therapy-naive adults were randomized to receive either ZIAGEN (300 mg  
 600 twice daily) plus COMBIVIR<sup>®</sup> (lamivudine 150 mg/zidovudine 300 mg twice daily), or indinavir  
 601 (800 mg 3 times a day) plus COMBIVIR twice daily. The study was stratified at randomization  
 602 by pre-entry plasma HIV-1 RNA 10,000 to 100,000 copies/mL and plasma HIV-1 RNA greater  
 603 than 100,000 copies/mL. Study participants were male (87%), Caucasian (73%), black (15%),  
 604 and Hispanic (9%). At baseline the median age was 36 years, the median baseline CD4+ cell  
 605 count was 360 cells/mm<sup>3</sup>, and median baseline plasma HIV-1 RNA was 4.8 log<sub>10</sub> copies/mL.  
 606 Proportions of patients with plasma HIV-1 RNA less than 400 copies/mL (using Roche  
 607 AMPLICOR HIV-1 MONITOR Test) through 48 weeks of treatment are summarized in Table 8.  
 608

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

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

610 <sup>a</sup> Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL.

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

612 <sup>c</sup> Includes consent withdrawn, lost to follow up, protocol violations, those with missing data,  
613 clinical progression, and other.

614

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

616

617 **Table 9. Proportions of Responders Through Week 48 By Screening Plasma HIV-1 RNA**  
618 **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

619

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

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

628 CNA30021 was an international, multicenter, double-blind, controlled study in which  
629 770 HIV-1-infected, therapy-naive adults were randomized and received either abacavir 600 mg  
630 once daily or abacavir 300 mg twice daily, both in combination with lamivudine 300 mg once  
631 daily and efavirenz 600 mg once daily. The double-blind treatment duration was at least  
632 48 weeks. Study participants had a mean age of 37 years, were: male (81%), Caucasian (54%),  
633 black (27%), and American Hispanic (15%). The median baseline CD4+ cell count was  
634 262 cells/mm<sup>3</sup> (range 21 to 918 cells/mm<sup>3</sup>) and the median baseline plasma HIV-1 RNA was  
635 4.89 log<sub>10</sub> copies/mL (range: 2.60 to 6.99 log<sub>10</sub> copies/mL).

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

637

638 **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 <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%

639 <sup>a</sup> Patients achieved and maintained confirmed HIV-1 RNA <50 copies/mL (<400 copies/mL)  
 640 through Week 48 (Roche AMPLICOR Ultrasensitive HIV-1 MONITOR standard test version  
 641 1.0).

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

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

646

647 After 48 weeks of therapy, the median CD4+ cell count increases from baseline were  
 648 188 cells/mm<sup>3</sup> in the group receiving abacavir 600 mg once daily and 200 cells/mm<sup>3</sup> in the group  
 649 receiving abacavir 300 mg twice daily. Through Week 48, 6 subjects (2%) in the group receiving  
 650 ZIAGEN 600 mg once daily (4 CDC classification C events and 2 deaths) and 10 subjects (3%)  
 651 in the group receiving ZIAGEN 300 mg twice daily (7 CDC classification C events and 3 deaths)  
 652 experienced clinical disease progression. None of the deaths were attributed to study  
 653 medications.

654 **14.2 Pediatric Patients**

655 Therapy-Experienced Pediatric Patients: CNA3006 was a randomized, double-blind  
 656 study comparing ZIAGEN 8 mg/kg twice daily plus lamivudine 4 mg/kg twice daily plus  
 657 zidovudine 180 mg/m<sup>2</sup> twice daily versus lamivudine 4 mg/kg twice daily plus zidovudine  
 658 180 mg/m<sup>2</sup> twice daily. Two hundred and five therapy-experienced pediatric patients were  
 659 enrolled: female (56%), Caucasian (17%), black (50%), Hispanic (30%), median age of  
 660 5.4 years, baseline CD4+ cell percent greater than 15% (median = 27%), and median baseline  
 661 plasma HIV-1 RNA of 4.6 log<sub>10</sub> copies/mL. Eighty percent and 55% of patients had prior  
 662 therapy with zidovudine and lamivudine, respectively, most often in combination. The median  
 663 duration of prior nucleoside analogue therapy was 2 years. At 16 weeks the proportion of  
 664 patients responding based on plasma HIV-1 RNA less than or equal to 400 copies/mL was  
 665 significantly higher in patients receiving ZIAGEN plus lamivudine plus zidovudine compared  
 666 with patients receiving lamivudine plus zidovudine, 13% versus 2%, respectively. Median  
 667 plasma HIV-1 RNA changes from baseline were -0.53 log<sub>10</sub> copies/mL in the group receiving  
 668 ZIAGEN plus lamivudine plus zidovudine compared with -0.21 log<sub>10</sub> copies/mL in the group  
 669 receiving lamivudine plus zidovudine. Median CD4+ cell count increases from baseline were

670 69 cells/mm<sup>3</sup> in the group receiving ZIAGEN plus lamivudine plus zidovudine and 9 cells/mm<sup>3</sup>  
671 in the group receiving lamivudine plus zidovudine.

## 672 **15 REFERENCES**

673 1. Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study Group. *Lancet*.  
674 2008;371 (9622):1417-1426.

## 675 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

678 They are packaged as follows:

679 Bottles of 60 tablets (NDC 49702-221-18).

680 Unit dose blister packs of 60 tablets (NDC 49702-221-44). Each pack contains 6 blister  
681 cards of 10 tablets each.

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

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

686 Bottles of 240 mL (NDC 49702-222-48) with child-resistant closure. This product does  
687 not require reconstitution.

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

## 690 **17 PATIENT COUNSELING INFORMATION**

691 See FDA-approved patient labeling (Medication Guide)

### 692 **17.1 Information About Therapy With ZIAGEN**

693 Hypersensitivity Reaction: Inform patients:

- 694 • that a Medication Guide and Warning Card summarizing the symptoms of the abacavir  
695 hypersensitivity reaction and other product information will be dispensed by the pharmacist  
696 with each new prescription and refill of ZIAGEN, and encourage the patient to read the  
697 Medication Guide and Warning Card every time to obtain any new information that may be  
698 present about ZIAGEN. (The complete text of the Medication Guide is reprinted at the end  
699 of this document.)
- 700 • to carry the Warning Card with them.
- 701 • how to identify a hypersensitivity reaction [*see Medication Guide*].
- 702 • that if they develop symptoms consistent with a hypersensitivity reaction they should call  
703 their doctor right away to determine if they should stop taking ZIAGEN.
- 704 • that a hypersensitivity reaction can worsen and lead to hospitalization or death if ZIAGEN is  
705 not immediately discontinued.
- 706 • that in one study, more severe hypersensitivity reactions were seen when ZIAGEN was  
707 dosed 600 mg once daily.

- 708 • to not restart ZIAGEN or any other abacavir-containing product following a hypersensitivity  
709 reaction because more severe symptoms can occur within hours and may include  
710 life-threatening hypotension and death.
- 711 • that a hypersensitivity reaction is usually reversible if it is detected promptly and ZIAGEN  
712 is stopped right away.
- 713 • that if they have interrupted ZIAGEN for reasons other than symptoms of hypersensitivity  
714 (for example, those who have an interruption in drug supply), a serious or fatal  
715 hypersensitivity reaction may occur with reintroduction of abacavir.
- 716 • to not restart ZIAGEN or any other abacavir-containing product without medical  
717 consultation and that restarting abacavir needs to be undertaken only if medical care can be  
718 readily accessed by the patient or others.
- 719 • ZIAGEN should not be coadministered with EPZICOM<sup>®</sup> (abacavir sulfate and lamivudine)  
720 Tablets or TRIZIVIR<sup>®</sup> (abacavir sulfate, lamivudine, and zidovudine) Tablets.

721 Lactic Acidosis/Hepatomegaly: Inform patients that some HIV medicines, including  
722 ZIAGEN, can cause a rare, but serious condition called lactic acidosis with liver enlargement  
723 (hepatomegaly) [*see Boxed Warning, Warnings and Precautions (5.2)*].

724 Redistribution/Accumulation of Body Fat: Inform patients that redistribution or  
725 accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause  
726 and long-term health effects of these conditions are not known at this time [*see Warnings and*  
727 *Precautions (5.4)*].

728 Information About HIV-1 Infection: ZIAGEN is not a cure for HIV-1 infection and  
729 patients may continue to experience illnesses associated with HIV-1 infection, including  
730 opportunistic infections. Patients should remain under the care of a physician when using  
731 ZIAGEN.

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

- 733 • **Do not share needles or other injection equipment.**
- 734 • **Do not share personal items that can have blood or body fluids on them, like**  
735 **toothbrushes and razor blades.**
- 736 • **Do not have any kind of sex without protection.** Always practice safe sex by using a  
737 latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal  
738 secretions, or blood.
- 739 • **Do not breastfeed.** We do not know if ZIAGEN can be passed to your baby in your  
740 breast milk and whether it could harm your baby. Also, mothers with HIV-1 should not  
741 breastfeed because HIV-1 can be passed to the baby in the breast milk.

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

743

744 COMBIVIR, EPIVIR, EPZICOM, TRIZIVIR, and ZIAGEN are registered trademarks of ViiV  
745 Healthcare.

746

747



748 Manufactured for:



749 ViiV Healthcare  
750 Research Triangle Park, NC 27709

751  
752  
753 by:



754 GlaxoSmithKline  
755 Research Triangle Park, NC 27709

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759  
760 ZGN:PI

## 761 MEDICATION GUIDE

### 762 763 ZIAGEN® (ZY-uh-jen) 764 (abacavir sulfate) 765 Tablets and Oral Solution

766  
767  
768 Read this Medication Guide before you start taking ZIAGEN and each time you get a  
769 refill. There may be new information. This information does not take the place of  
770 talking to your healthcare provider about your medical condition or your treatment.  
771 Be sure to carry your ZIAGEN Warning Card with you at all times.

#### 772 773 **What is the most important information I should know about ZIAGEN?**

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

780 **If you get a symptom from 2 or more of the following groups while**  
781 **taking ZIAGEN, call your healthcare provider right away to find out if**  
782 **you should stop taking ZIAGEN.**

783

	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

784

785 A list of these symptoms is on the Warning Card your pharmacist gives you.

786 **Carry this Warning Card with you at all times.**

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

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

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

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

- 806 • you feel very weak or tired
- 807 • you have unusual (not normal) muscle pain
- 808 • you have trouble breathing
- 809 • you have stomach pain with nausea and vomiting
- 810 • you feel cold, especially in your arms and legs
- 811 • you feel dizzy or light-headed
- 812 • you have a fast or irregular heartbeat

813 **3. Serious liver problems. Some people who have taken medicines like**  
814 **ZIAGEN have developed serious liver problems called hepatotoxicity,**  
815 **with liver enlargement (hepatomegaly) and fat in the liver (steatosis).**  
816 **Hepatomegaly with steatosis is a serious medical emergency that can**  
817 **cause death.**

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

- 820 • your skin or the white part of your eyes turns yellow (jaundice)
- 821 • your urine turns dark
- 822 • your bowel movements (stools) turn light in color
- 823 • you don't feel like eating food for several days or longer
- 824 • you feel sick to your stomach (nausea)
- 825 • you have lower stomach area (abdominal) pain

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

829

### 830 **What is ZIAGEN?**

831 ZIAGEN is a prescription medicine used to treat HIV infection. ZIAGEN is a medicine  
832 called a nucleoside analogue reverse transcriptase inhibitor (NRTI). ZIAGEN is  
833 always used with other anti-HIV medicines. When used in combination with these  
834 other medicines, ZIAGEN helps lower the amount of HIV in your blood.

- 835 • **ZIAGEN does not cure HIV infection or AIDS.**
- 836 • It is not known if ZIAGEN will help you live longer or have fewer of the medical  
837 problems that people get with HIV or AIDS.
- 838 • It is very important that you see your doctor regularly while you are taking  
839 ZIAGEN.

840

### 841 **Who should not take ZIAGEN?**

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

- 843 • **are allergic to abacavir or any of the ingredients in ZIAGEN. See the**  
844 **end of this Medication Guide for a complete list of ingredients in**  
845 **ZIAGEN.**
- 846 • **have certain liver problems.**

### 847 **What should I tell my healthcare provider before taking ZIAGEN?**

848 **Before you take ZIAGEN, tell your healthcare provider if you:**

- 849 • **have been tested and know whether or not you have a particular gene**
- 850 **variation called HLA-B\*5701**
- 851 • **have hepatitis B virus infection or have other liver problems**
- 852 • **have heart problems, smoke, or have diseases that increase your risk**
- 853 **of heart disease such as high blood pressure, high cholesterol, or**
- 854 **diabetes.**
- 855 • **are pregnant or plan to become pregnant.** It is not known if ZIAGEN will
- 856 harm your unborn baby. Talk to your healthcare provider if you are pregnant or
- 857 plan to become pregnant.
- 858 • **Pregnancy Registry.** If you take ZIAGEN while you are pregnant, talk to your
- 859 healthcare provider about how you can take part in the Pregnancy Registry for
- 860 ZIAGEN. The purpose of the pregnancy registry is to collect information about
- 861 the health of you and your baby.
- 862 • **are breastfeeding or plan to breastfeed. Do not breastfeed.** We do not
- 863 know if ZIAGEN can be passed to your baby in your breast milk and whether it
- 864 could harm your baby. Also, mothers with HIV-1 should not breastfeed because
- 865 HIV-1 can be passed to the baby in the breast milk.
- 866 • **Tell your healthcare provider about all the medicines you take,** including
- 867 prescription and nonprescription medicines, vitamins, and herbal supplements.
- 868 **Especially tell your healthcare provider if you take:**
- 869 • alcohol
- 870 • methadone
- 871 • TRIZIVIR (abacavir sulfate, lamivudine, and zidovudine)
- 872 • EPZICOM (abacavir sulfate and lamivudine)
- 873 Ask your healthcare provider if you are not sure if you take one of the medicines
- 874 listed above.
- 875 ZIAGEN may affect the way other medicines work, and other medicines may affect
- 876 how ZIAGEN works.
- 877 Know the medicines you take. Keep a list of your medicines with you to show to
- 878 your healthcare provider and pharmacist when you get a new medicine.
- 879
- 880 **How should I take ZIAGEN?**
- 881 • **Take ZIAGEN exactly as your healthcare provider tells you to take it.**
- 882 • **ZIAGEN is taken by mouth as a tablet or a strawberry- and**
- 883 **banana-flavored liquid.**
- 884 • ZIAGEN may be taken with or without food.
- 885 • Do not skip doses.

- 886 • Children aged 3 months and older can also take ZIAGEN. The child’s healthcare  
887 provider will decide the right dose and whether the child should take the tablet  
888 or liquid, based on the child’s weight. The dose should not be more than the  
889 recommended adult dose.
- 890 • **Do not let your ZIAGEN run out.**  
891 If you stop your anti-HIV medicines, even for a short time, the amount of virus  
892 in your blood may increase and the virus may become harder to treat. If you  
893 take too much ZIAGEN, call your healthcare provider or poison control center or  
894 go to the nearest hospital emergency room right away.

895

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

- 897 • **ZIAGEN can cause serious side effects including allergic reactions, lactic**  
898 **acidosis, and liver problems. See “What is the most important**  
899 **information I should know about ZIAGEN?”**
- 900 • **Changes in immune system (Immune Reconstitution Syndrome).** Your  
901 immune system may get stronger and begin to fight infections that have been  
902 hidden in your body for a long time. Tell your healthcare provider if you start  
903 having new or worse symptoms of infection after you start taking ZIAGEN.
- 904 • **Changes in body fat (fat redistribution).** Changes in body fat (lipoatrophy or  
905 lipodystrophy) can happen in some people taking antiretroviral medicines  
906 including ZIAGEN.  
907 These changes may include:
- 908 • more fat in or around your trunk, upper back and neck (buffalo hump),  
909 breast, or chest
  - 910 • loss of fat in your legs, arms, or face
- 911 • **Heart attack (myocardial infarction).** Some HIV medicines including ZIAGEN  
912 may increase your risk of heart attack.

### 913 **The most common side effects of ZIAGEN in adults include:**

- 914 • bad dreams or sleep problems
- 915 • nausea
- 916 • headache
- 917 • tiredness
- 918 • vomiting

### 919 **The most common side effects of ZIAGEN in children include:**

- 920 • fever and chills
- 921 • nausea

- 922 • vomiting
- 923 • rash
- 924 • ear, nose, or throat infections

925  
926 Tell your healthcare provider if you have any side effect that bothers you or that  
927 does not go away.

928 These are not all the possible side effects of ZIAGEN. For more information, ask  
929 your healthcare provider or pharmacist.

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

932  
933 **How should I store ZIAGEN?**

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

937  
938 **General information for safe and effective use of ZIAGEN**

939 Avoid doing things that can spread HIV-1 infection to others.

- 940 • **Do not share needles or other injection equipment.**
- 941 • **Do not share personal items that can have blood or body fluids on**  
942 **them, like toothbrushes and razor blades.**
- 943 • **Do not have any kind of sex without protection.** Always practice safe sex  
944 by using a latex or polyurethane condom to lower the chance of sexual contact  
945 with semen, vaginal secretions, or blood.

946  
947 Medicines are sometimes prescribed for purposes other than those listed in a  
948 Medication Guide. Do not use ZIAGEN for a condition for which it was not  
949 prescribed. Do not give ZIAGEN to other people, even if they have the same  
950 symptoms that you have. It may harm them.

951  
952 This Medication Guide summarizes the most important information about ZIAGEN.  
953 If you would like more information, talk with your healthcare provider. You can ask  
954 your healthcare provider or pharmacist for the information that is written for  
955 healthcare professionals.

956  
957 For more information go to [www.ZIAGEN.com](http://www.ZIAGEN.com) or call 1-877-844-8872.

958  
959 **What are the ingredients in ZIAGEN?**

960 **Tablets**

961 Active ingredient: abacavir sulfate

962 Inactive ingredients: colloidal silicon dioxide, magnesium stearate, microcrystalline  
963 cellulose, and sodium starch glycolate, and a film-coating made of hypromellose,  
964 polysorbate 80, synthetic yellow iron oxide, titanium dioxide, and triacetin.

965 **Oral Solution:**

966 Active ingredient: abacavir sulfate

967 Inactive ingredients: artificial strawberry and banana flavors, citric acid  
968 (anhydrous), methylparaben and propylparaben (added as preservatives),  
969 propylene glycol, saccharin sodium, sodium citrate (dihydrate), sorbitol solution,  
970 and water.

971  
972 This Medication Guide has been approved by the US Food and Drug Administration.

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974

975

976 Manufactured for:



977

978 ViiV Healthcare

979 Research Triangle Park, NC 27709

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981 by:



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983 GlaxoSmithKline

984 Research Triangle Park, NC 27709

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