

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)

-----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, functionally scored (3)

- Oral Solution: 20 mg per 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 greater than or equal to 10%) in adult HIV-1 clinical trials 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 greater than or equal to 5%) in pediatric HIV-1 clinical trials 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.

-----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)

-----USE IN SPECIFIC POPULATIONS-----

- Lactation: Breastfeeding not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 02/2015

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1 **FULL PRESCRIBING INFORMATION**

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

4 **Hypersensitivity Reactions**

5 **Serious and sometimes fatal hypersensitivity reactions have been associated with ZIAGEN[®]**
6 **(abacavir sulfate).**

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

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

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

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

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

30 **Lactic Acidosis and Severe Hepatomegaly**

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

34 **1 INDICATIONS AND USAGE**

35 ZIAGEN tablets and oral solution, in combination with other antiretroviral agents, are indicated
36 for the treatment of human immunodeficiency virus (HIV-1) infection.

37 Additional important information on the use of ZIAGEN for treatment of HIV-1 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 • ZIAGEN may be taken with or without food.

46 **2.1 Adult Patients**

47 The recommended oral dose of ZIAGEN for adults is 600 mg daily, administered as either
48 300 mg twice daily or 600 mg once daily, in combination with other antiretroviral agents.

49 **2.2 Pediatric Patients**

50 The recommended oral dose of ZIAGEN oral solution in HIV-1-infected pediatric patients aged
51 3 months and older is 8 mg per kg twice daily (up to a maximum of 300 mg twice daily) in
52 combination with other antiretroviral agents.

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

59 **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

60

61 **2.3 Patients with Hepatic Impairment**

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

67 **3 DOSAGE FORMS AND STRENGTHS**

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

71 ZIAGEN oral solution contains 20 mg per mL of abacavir as abacavir sulfate. The solution is a
72 clear to opalescent, yellowish, strawberry-banana-flavored liquid.

73 **4 CONTRAINDICATIONS**

74 ZIAGEN is contraindicated in patients with:

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

80 **5 WARNINGS AND PRECAUTIONS**

81 **5.1 Hypersensitivity Reaction**

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

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

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

100 Group 1: Fever

101 Group 2: Rash

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

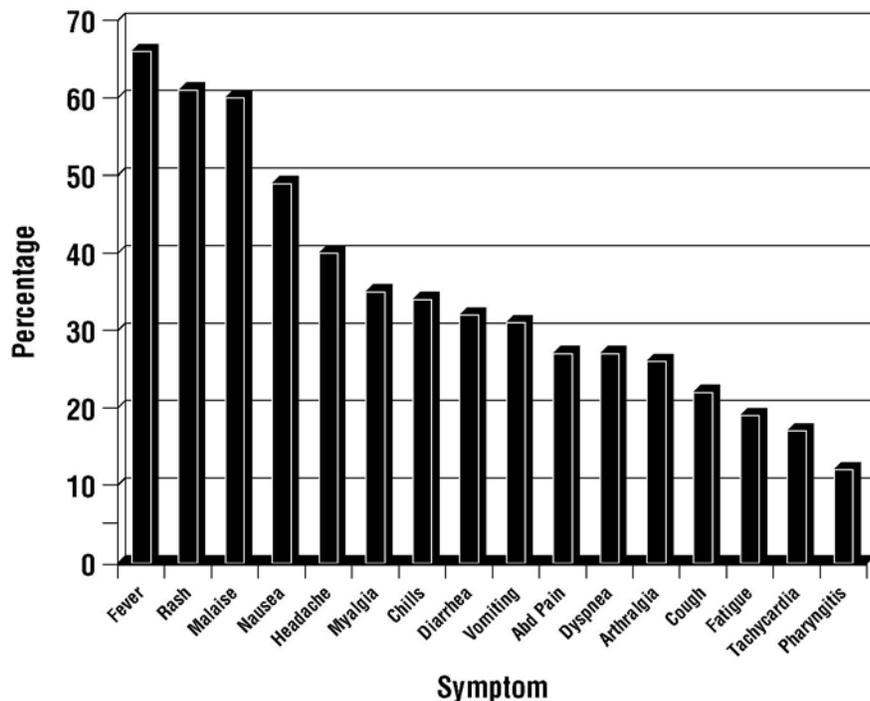
103 Group 4: Constitutional (including generalized malaise, fatigue, or achiness)

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

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

107 Hypersensitivity to abacavir was reported in approximately 8% of 2,670 subjects (n = 206) in
108 9 clinical trials (range: 2% to 9%) with enrollment from November 1999 to February 2002. Data
109 on time to onset and symptoms of suspected hypersensitivity were collected on a detailed data
110 collection module. The frequencies of symptoms are shown in Figure 1. Symptoms usually
111 appeared within the first 6 weeks of treatment with abacavir, although the reaction may occur at
112 any time during therapy. Median time to onset was 9 days; 89% appeared within the first
113 6 weeks; 95% of subjects reported symptoms from 2 or more of the 5 groups listed above.

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



116
 117 Other less common signs and symptoms of hypersensitivity include lethargy, myolysis, edema,
 118 abnormal chest x-ray findings (predominantly infiltrates, which can be localized), and
 119 paresthesia. Anaphylaxis, liver failure, renal failure, hypotension, adult respiratory distress
 120 syndrome, respiratory failure, and death have occurred in association with hypersensitivity
 121 reactions. In one trial, 4 subjects (11%) receiving ZIAGEN 600 mg once daily experienced
 122 hypotension with a hypersensitivity reaction compared with 0 subjects receiving ZIAGEN
 123 300 mg twice daily.

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

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

132 **Clinical Management of Hypersensitivity**

133 Discontinue ZIAGEN as soon as a hypersensitivity reaction is suspected. To minimize the risk of
 134 a life-threatening hypersensitivity reaction, permanently discontinue ZIAGEN if hypersensitivity
 135 cannot be ruled out, even when other diagnoses are possible (e.g., acute onset respiratory

136 diseases such as pneumonia, bronchitis, pharyngitis, or influenza; gastroenteritis; or reactions to
137 other medications).

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

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

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

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

156 Risk Factor

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

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

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

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

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

180 **5.2 Lactic Acidosis/Severe Hepatomegaly with Steatosis**

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

190 **5.3 Immune Reconstitution Syndrome**

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

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

200 **5.4 Fat Redistribution**

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

206 **5.5 Myocardial Infarction**

207 In a published prospective, observational, epidemiological trial designed to investigate the rate of
208 myocardial infarction in patients on combination antiretroviral therapy, the use of abacavir

209 within the previous 6 months was correlated with an increased risk of myocardial infarction
210 (MI).¹ In a sponsor-conducted pooled analysis of clinical trials, no excess risk of myocardial
211 infarction was observed in abacavir-treated subjects as compared with control subjects. In
212 totality, the available data from the observational cohort and from clinical trials are inconclusive.

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

216 **6 ADVERSE REACTIONS**

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

- 218 • Serious and sometimes fatal hypersensitivity reaction. In one trial, once-daily dosing of
219 abacavir was associated with more severe hypersensitivity reactions [*see Boxed Warning,*
220 *Warnings and Precautions (5.1)*].
- 221 • Lactic acidosis and severe hepatomegaly [*see Boxed Warning, Warnings and Precautions*
222 *(5.2)*].
- 223 • Immune reconstitution syndrome [*see Warnings and Precautions (5.3)*].
- 224 • Fat redistribution [*see Warnings and Precautions (5.4)*].
- 225 • Myocardial infarction [*see Warnings and Precautions (5.5)*].

226 **6.1 Clinical Trials Experience**

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

230 Adults

231 *Therapy-naive Adults:* Treatment-emergent clinical adverse reactions (rated by the investigator
232 as moderate or severe) with a greater than or equal to 5% frequency during therapy with
233 ZIAGEN 300 mg twice daily, lamivudine 150 mg twice daily, and efavirenz 600 mg daily
234 compared with zidovudine 300 mg twice daily, lamivudine 150 mg twice daily, and efavirenz
235 600 mg daily from CNA30024 are listed in Table 2.

236 **Table 2. Treatment-emergent (All Causality) Adverse Reactions of at Least Moderate**
 237 **Intensity (Grades 2-4, Greater than or Equal to 5% Frequency) in Therapy-naive Adults**
 238 **(CNA30024^a) through 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% ^b
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%

239 ^a This trial used double-blind ascertainment of suspected hypersensitivity reactions. During the
 240 blinded portion of the trial, suspected hypersensitivity to abacavir was reported by investigators
 241 in 9% of 324 subjects in the abacavir group and 3% of 325 subjects in the zidovudine group.

242 ^b Ten (3%) cases of suspected drug hypersensitivity were reclassified as not being due to
 243 abacavir following unblinding.

244 Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe)
 245 with a greater than or equal to 5% frequency during therapy with ZIAGEN 300 mg twice daily,
 246 lamivudine 150 mg twice daily, and zidovudine 300 mg twice daily compared with indinavir
 247 800 mg 3 times daily, lamivudine 150 mg twice daily, and zidovudine 300 mg twice daily from
 248 CNA3005 are listed in Table 3.

249 **Table 3. Treatment-emergent (All Causality) Adverse Reactions of at Least Moderate**
 250 **Intensity (Grades 2-4, Greater than or Equal to 5% Frequency) in Therapy-naive Adults**
 251 **(CNA3005) through 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%

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

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

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

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

272 **Table 4. Laboratory Abnormalities (Grades 3-4) in Therapy-naive Adults (CNA30024)**
 273 **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 ³)	2%	4%
Anemia (Hgb ≤6.9 gm/dL)	<1%	2%
Thrombocytopenia (Platelets <50,000/mm ³)	1%	<1%
Leukopenia (WBC ≤1,500/mm ³)	<1%	2%

274 ULN = Upper limit of normal.

275 n = Number of subjects assessed.

276 Laboratory abnormalities in CNA3005 are listed in Table 5.

277 **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 ³)	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%)

278 ULN = Upper limit of normal.

279 n = Number of subjects assessed.

280 The frequencies of treatment-emergent laboratory abnormalities were comparable between
 281 treatment groups in CNA30021.

282 Pediatric Trials

283 *Therapy-experienced Pediatric Subjects:* Treatment-emergent clinical adverse reactions
284 (rated by the investigator as moderate or severe) with a greater than or equal to 5% frequency
285 during therapy with ZIAGEN 8 mg per kg twice daily, lamivudine 4 mg per kg twice daily, and
286 zidovudine 180 mg per m² twice daily compared with lamivudine 4 mg per kg twice daily and
287 zidovudine 180 mg per m² twice daily from CNA3006 are listed in Table 6.

288 **Table 6. Treatment-emergent (All Causality) Adverse Reactions of at Least Moderate**
289 **Intensity (Grades 2-4, Greater than or Equal to 5% Frequency) in Therapy-experienced**
290 **Pediatric Subjects (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%

291

292 *Laboratory Abnormalities:* In CNA3006, laboratory abnormalities (anemia, neutropenia, liver
293 function test abnormalities, and CPK elevations) were observed with similar frequencies as in a
294 trial of therapy-naive adults (CNA30024). Mild elevations of blood glucose were more frequent
295 in pediatric subjects receiving ZIAGEN (CNA3006) as compared with adult subjects
296 (CNA30024).

297 Other Adverse Events

298 In addition to adverse reactions and laboratory abnormalities reported in Tables 2, 3, 4, 5, and 6,
299 other adverse reactions observed in the expanded access program were pancreatitis and increased
300 GGT.

301 **6.2 Postmarketing Experience**

302 The following adverse reactions have been identified during post-approval use of ZIAGEN.
303 Because these reactions are reported voluntarily from a population of unknown size, it is not
304 always possible to reliably estimate their frequency or establish a causal relationship to drug
305 exposures. These reactions have been chosen for inclusion due to a combination of their
306 seriousness, frequency of reporting, or potential causal connection to ZIAGEN.

307 Body as a Whole

308 Redistribution/accumulation of body fat.

309 Cardiovascular

310 Myocardial infarction.

311 Hepatic

312 Lactic acidosis and hepatic steatosis.

313 Skin

314 Suspected Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been
315 reported in patients receiving abacavir primarily in combination with medications known to be
316 associated with SJS and TEN, respectively. Because of the overlap of clinical signs and
317 symptoms between hypersensitivity to abacavir and SJS and TEN, and the possibility of multiple
318 drug sensitivities in some patients, abacavir should be discontinued and not restarted in such
319 cases.

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

321 **7 DRUG INTERACTIONS**

322 **7.1 Ethanol**

323 Abacavir has no effect on the pharmacokinetic properties of ethanol. Ethanol decreases the
324 elimination of abacavir causing an increase in overall exposure [*see Clinical Pharmacology*
325 (*12.3*)].

326 **7.2 Methadone**

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

333 **8 USE IN SPECIFIC POPULATIONS**

334 **8.1 Pregnancy**

335 Pregnancy Exposure Registry

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

339 Risk Summary

340 Available data from the Antiretroviral Pregnancy Registry show no difference in the risk of
341 overall major birth defects for abacavir compared with the background rate for major birth

342 defects of 2.7% in the US reference population of the Metropolitan Atlanta Congenital Defects
343 Program (MACDP). Abacavir produced fetal malformations and other embryonic and fetal
344 toxicities in rats at 35 times the human exposure at the recommended clinical dose. The
345 relevance of animal findings to human pregnancy registry data is not known.

346 Data

347 *Human Data:* Based on prospective reports from the Antiretroviral Pregnancy Registry of over
348 2,000 exposures to abacavir during pregnancy resulting in live births (including over 900
349 exposed in the first trimester), there was no difference between abacavir and overall birth defects
350 compared with the background birth defect rate of 2.7% in the US reference population of the
351 MACDP. The prevalence of defects in the first trimester was 3.0% (95% CI: 2.0% to 4.4%).

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

361 **8.2 Lactation**

362 Risk Summary

363 The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the
364 United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1
365 infection. Because of the potential for HIV-1 transmission, mothers should be instructed not to
366 breastfeed.

367 **8.4 Pediatric Use**

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

373 **8.5 Geriatric Use**

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

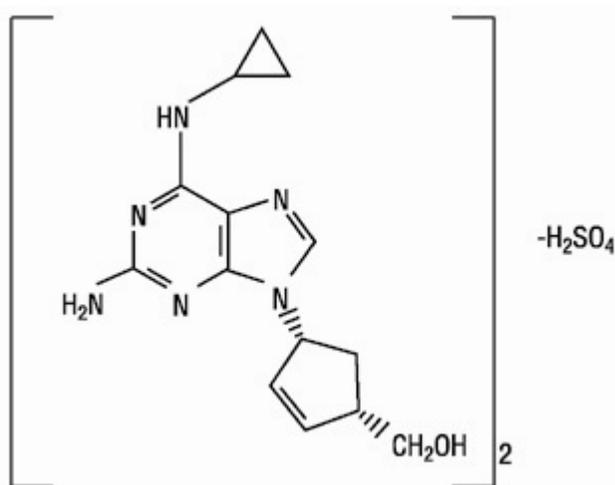
378 **10 OVERDOSAGE**

379 There is no known antidote for ZIAGEN. It is not known whether abacavir can be removed by
380 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 (C₁₄H₁₈N₆O)₂•H₂SO₄ and a molecular weight of
387 670.76 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 77 mg per mL in
392 distilled water at 25°C. It has an octanol per water (pH 7.1 to 7.3) partition coefficient (log *P*) of
393 approximately 1.20 at 25°C.

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

399 ZIAGEN oral solution is for oral administration. Each milliliter (1 mL) of ZIAGEN oral solution
400 contains abacavir sulfate equivalent to 20 mg of abacavir (i.e., 20 mg per 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 are
405 expressed in terms of abacavir.

406 **12 CLINICAL PHARMACOLOGY**

407 **12.1 Mechanism of Action**

408 Abacavir is an antiviral agent [See Microbiology (12.4)].

409 **12.3 Pharmacokinetics**

410 Pharmacokinetics in Adults

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

415 *Absorption and Bioavailability:* Abacavir was rapidly and extensively absorbed after oral
416 administration. The geometric mean absolute bioavailability of the tablet was 83%. After oral
417 administration of 300 mg twice daily in 20 subjects, the steady-state peak serum abacavir
418 concentration (C_{max}) was 3.0 ± 0.89 mcg per mL (mean \pm SD) and $AUC_{(0-12\text{ h})}$ was
419 6.02 ± 1.73 mcg•hour per mL. After oral administration of a single dose of 600 mg of abacavir in
420 20 subjects, C_{max} was 4.26 ± 1.19 mcg per mL (mean \pm SD) and AUC_{∞} was
421 11.95 ± 2.51 mcg•hour per mL.

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

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

429 *Metabolism:* In humans, abacavir is not significantly metabolized by cytochrome P450
430 enzymes. The primary routes of elimination of abacavir are metabolism by alcohol
431 dehydrogenase (to form the 5'-carboxylic acid) and glucuronyl transferase (to form the
432 5'-glucuronide). The metabolites do not have antiviral activity. In vitro experiments reveal that
433 abacavir does not inhibit human CYP3A4, CYP2D6, or CYP2C9 activity at clinically relevant
434 concentrations.

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

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

442 Effects of Food on Oral Absorption

443 Bioavailability of abacavir tablets was assessed in the fasting and fed states. There was no
444 significant difference in systemic exposure (AUC_{∞}) in the fed and fasting states; therefore,
445 ZIAGEN tablets may be administered with or without food. Systemic exposure to abacavir was
446 comparable after administration of ZIAGEN oral solution and ZIAGEN tablets. Therefore, these
447 products may be used interchangeably.

448 Special Populations

449 *Renal Impairment:* The pharmacokinetic properties of ZIAGEN have not been determined in
450 patients with impaired renal function. Renal excretion of unchanged abacavir is a minor route of
451 elimination in humans.

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

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

469 *Geriatric Patients:* The pharmacokinetics of ZIAGEN have not been studied in subjects over
470 65 years of age.

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

474 *Race:* There are no significant differences between blacks and whites in abacavir
475 pharmacokinetics.

476 Drug Interactions

477 In human liver microsomes, abacavir did not inhibit cytochrome P450 isoforms (2C9, 2D6,
478 3A4). Based on these data, it is unlikely that clinically significant drug interactions will occur
479 between abacavir and drugs metabolized through these pathways.

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

488 *Ethanol:* Due to the common metabolic pathways of abacavir and ethanol via alcohol
489 dehydrogenase, the pharmacokinetic interaction between abacavir and ethanol was studied in
490 24 HIV-1-infected male subjects. Each subject received the following treatments on separate
491 occasions: a single 600-mg dose of abacavir, 0.7 g per kg ethanol (equivalent to 5 alcoholic
492 drinks), and abacavir 600 mg plus 0.7 g per kg ethanol. Coadministration of ethanol and abacavir
493 resulted in a 41% increase in abacavir AUC_∞ and a 26% increase in abacavir t_{1/2}. In males,
494 abacavir had no effect on the pharmacokinetic properties of ethanol, so no clinically significant
495 interaction is expected in men. This interaction has not been studied in females.

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

502 **12.4 Microbiology**

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

511 Antiviral Activity

512 The antiviral activity of abacavir against HIV-1 was evaluated against a T-cell tropic laboratory
513 strain HIV-1_{IIIB} in lymphoblastic cell lines, a monocyte/macrophage tropic laboratory strain
514 HIV-1_{BaL} in primary monocytes/macrophages, and clinical isolates in peripheral blood
515 mononuclear cells. The concentration of drug necessary to effect viral replication by 50 percent
516 (EC₅₀) ranged from 3.7 to 5.8 μM (1 μM = 0.28 mcg per mL) and 0.07 to 1.0 μM against
517 HIV-1_{IIIB} and HIV-1_{BaL}, respectively, and was 0.26 ± 0.18 μM against 8 clinical isolates. The
518 EC₅₀ values of abacavir against different HIV-1 clades (A-G) ranged from 0.0015 to 1.05 μM,
519 and against HIV-2 isolates, from 0.024 to 0.49 μM. The antiviral activity of abacavir in cell
520 culture was not antagonized when combined with the nucleoside reverse transcriptase inhibitors
521 (NRTIs) didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine or zidovudine,
522 the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, or the protease inhibitor
523 (PI) amprenavir. Ribavirin (50 μM) had no effect on the anti-HIV-1 activity of abacavir in cell
524 culture.

525 Resistance

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

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

542 Cross-resistance

543 Cross-resistance has been observed among NRTIs. Isolates containing abacavir
544 resistance-associated substitutions, namely, K65R, L74V, Y115F, and M184V, exhibited
545 cross-resistance to didanosine, emtricitabine, lamivudine, tenofovir, and zalcitabine in cell
546 culture and in subjects. The K65R substitution can confer resistance to abacavir, didanosine,
547 emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine; the L74V substitution can confer
548 resistance to abacavir, didanosine, and zalcitabine; and the M184V substitution can confer
549 resistance to abacavir, didanosine, emtricitabine, lamivudine, and zalcitabine. An increasing

550 number of thymidine analogue mutations (TAMs: M41L, D67N, K70R, L210W, T215Y/F,
551 K219E/R/H/Q/N) is associated with a progressive reduction in abacavir susceptibility.

552 **13 NONCLINICAL TOXICOLOGY**

553 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

554 Carcinogenicity

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

563 Mutagenicity

564 Abacavir induced chromosomal aberrations both in the presence and absence of metabolic
565 activation in an in vitro cytogenetic study in human lymphocytes. Abacavir was mutagenic in the
566 absence of metabolic activation, although it was not mutagenic in the presence of metabolic
567 activation in an L5178Y mouse lymphoma assay. Abacavir was clastogenic in males and not
568 clastogenic in females in an in vivo mouse bone marrow micronucleus assay.

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

571 Impairment of Fertility

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

575 **13.2 Animal Toxicology and/or Pharmacology**

576 Myocardial degeneration was found in mice and rats following administration of abacavir for
577 2 years. The systemic exposures were equivalent to 7 to 24 times the expected systemic exposure
578 in humans. The clinical relevance of this finding has not been determined.

579 **14 CLINICAL STUDIES**

580 **14.1 Adult Trials**

581 Therapy-naive Adults

582 CNA30024 was a multicenter, double-blind, controlled trial in which 649 HIV-1-infected,
583 therapy-naive adults were randomized and received either ZIAGEN (300 mg twice daily),

584 lamivudine (150 mg twice daily), and efavirenz (600 mg once daily); or zidovudine (300 mg
 585 twice daily), lamivudine (150 mg twice daily), and efavirenz (600 mg once daily). The duration
 586 of double-blind treatment was at least 48 weeks. Trial participants were male (81%), white
 587 (51%), black (21%), and Hispanic (26%). The median age was 35 years; the median pretreatment
 588 CD4+ cell count was 264 cells per mm³, and median plasma HIV-1 RNA was 4.79 log₁₀ copies
 589 per mL. The outcomes of randomized treatment are provided in Table 7.

590 **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 ^a	69% (73%)	69% (71%)
Virologic failures ^b	6%	4%
Discontinued due to adverse reactions	14%	16%
Discontinued due to other reasons ^c	10%	11%

591 ^a Subjects achieved and maintained confirmed HIV-1 RNA less than or equal to 50 copies per
 592 mL (less than 400 copies per mL) through Week 48 (Roche AMPLICOR Ultrasensitive HIV-1
 593 MONITOR[®] standard test 1.0 PCR).

594 ^b Includes viral rebound, insufficient viral response according to the investigator, and failure to
 595 achieve confirmed less than or equal to 50 copies per mL by Week 48.

596 ^c Includes consent withdrawn, lost to follow up, protocol violations, those with missing data,
 597 clinical progression, and other.

598 After 48 weeks of therapy, the median CD4+ cell count increases from baseline were
 599 209 cells per mm³ in the group receiving ZIAGEN and 155 cells per mm³ in the zidovudine
 600 group. Through Week 48, 8 subjects (2%) in the group receiving ZIAGEN (5 CDC
 601 classification C events and 3 deaths) and 5 subjects (2%) on the zidovudine arm (3 CDC
 602 classification C events and 2 deaths) experienced clinical disease progression.

603 CNA3005 was a multicenter, double-blind, controlled trial in which 562 HIV-1-infected,
 604 therapy-naive adults were randomized to receive either ZIAGEN (300 mg twice daily) plus
 605 COMBIVIR[®] (lamivudine 150 mg/zidovudine 300 mg twice daily), or indinavir (800 mg 3 times
 606 a day) plus COMBIVIR twice daily. The trial was stratified at randomization by pre-entry
 607 plasma HIV-1 RNA 10,000 to 100,000 copies per mL and plasma HIV-1 RNA greater than
 608 100,000 copies per mL. Trial participants were male (87%), white (73%), black (15%), and
 609 Hispanic (9%). At baseline the median age was 36 years; the median baseline CD4+ cell count
 610 was 360 cells per mm³, and median baseline plasma HIV-1 RNA was 4.8 log₁₀ copies per mL.
 611 Proportions of subjects with plasma HIV-1 RNA less than 400 copies per mL (using Roche
 612 AMPLICOR HIV-1 MONITOR Test) through 48 weeks of treatment are summarized in Table 8.

613 **Table 8. Outcomes of Randomized Treatment through Week 48 (CNA3005)**

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

614 ^a Subjects achieved and maintained confirmed HIV-1 RNA less than 400 copies per mL.

615 ^b Includes viral rebound and failure to achieve confirmed less than 400 copies per mL by Week
616 48.

617 ^c Includes consent withdrawn, lost to follow up, protocol violations, those with missing data,
618 clinical progression, and other.

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

620 **Table 9. Proportions of Responders through Week 48 by Screening Plasma HIV-1 RNA**
621 **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

622 In subjects with baseline viral load greater than 100,000 copies per mL, percentages of subjects
623 with HIV-1 RNA levels less than 50 copies per mL were 31% in the group receiving abacavir
624 versus 45% in the group receiving indinavir.

625 Through Week 48, an overall mean increase in CD4+ cell count of about 150 cells per mm³ was
626 observed in both treatment arms. Through Week 48, 9 subjects (3.4%) in the group receiving
627 abacavir sulfate (6 CDC classification C events and 3 deaths) and 3 subjects (1.5%) in the group
628 receiving indinavir (2 CDC classification C events and 1 death) experienced clinical disease
629 progression.

630 CNA30021 was an international, multicenter, double-blind, controlled trial in which
631 770 HIV-1-infected, therapy-naïve adults were randomized and received either abacavir 600 mg
632 once daily or abacavir 300 mg twice daily, both in combination with lamivudine 300 mg once
633 daily and efavirenz 600 mg once daily. The double-blind treatment duration was at least
634 48 weeks. Trial participants had a mean age of 37 years; were male (81%), white (54%), black
635 (27%), and American Hispanic (15%). The median baseline CD4+ cell count was 262 cells per
636 mm³ (range: 21 to 918 cells per mm³) and the median baseline plasma HIV-1 RNA was
637 4.89 log₁₀ copies per mL (range: 2.60 to 6.99 log₁₀ copies per mL).

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

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

640 ^a Subjects achieved and maintained confirmed HIV-1 RNA less than 50 copies per mL (less than
641 400 copies per mL) through Week 48 (Roche AMPLICOR Ultrasensitive HIV-1 MONITOR
642 standard test version 1.0).

643 ^b Includes viral rebound, failure to achieve confirmed less than 50 copies per mL (less than
644 400 copies per mL) by Week 48, and insufficient viral load response.

645 ^c Includes consent withdrawn, lost to follow up, protocol violations, clinical progression, and
646 other.

647 After 48 weeks of therapy, the median CD4+ cell count increases from baseline were 188 cells
648 per mm³ in the group receiving abacavir 600 mg once daily and 200 cells per mm³ 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 trial medications.

653 **14.2 Pediatric Trials**

654 Therapy-experienced Pediatric Subjects

655 CNA3006 was a randomized, double-blind trial comparing ZIAGEN 8 mg per kg twice daily
656 plus lamivudine 4 mg per kg twice daily plus zidovudine 180 mg per m² twice daily versus
657 lamivudine 4 mg per kg twice daily plus zidovudine 180 mg per m² twice daily. Two hundred
658 and five therapy-experienced pediatric subjects were enrolled: female (56%), white (17%), black
659 (50%), Hispanic (30%), median age of 5.4 years, baseline CD4+ cell percent greater than 15%
660 (median = 27%), and median baseline plasma HIV-1 RNA of 4.6 log₁₀ copies per mL. Eighty
661 percent and 55% of subjects had prior therapy with zidovudine and lamivudine, respectively,
662 most often in combination. The median duration of prior nucleoside analogue therapy was
663 2 years. At 16 weeks the proportion of subjects responding based on plasma HIV-1 RNA less
664 than or equal to 400 copies per mL was significantly higher in subjects receiving ZIAGEN plus
665 lamivudine plus zidovudine compared with subjects receiving lamivudine plus zidovudine, 13%
666 versus 2%, respectively. Median plasma HIV-1 RNA changes from baseline were -0.53 log₁₀

667 copies per mL in the group receiving ZIAGEN plus lamivudine plus zidovudine compared with -
668 0.21 log₁₀ copies per mL in the group receiving lamivudine plus zidovudine. Median CD4+ cell
669 count increases from baseline were 69 cells per mm³ in the group receiving ZIAGEN plus
670 lamivudine plus zidovudine and 9 cells per mm³ in the group receiving lamivudine plus
671 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, functionally scored, capsule-shaped, film-coated, and imprinted with “GX 623” on
678 both sides. 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 cards of
681 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 liquid.
684 Each mL of the solution contains abacavir sulfate equivalent to 20 mg of abacavir. It is packaged
685 in plastic bottles as follows:

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

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

690 **17 PATIENT COUNSELING INFORMATION**

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

692 Hypersensitivity Reaction

693 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 instruct 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 of
699 this document.

- 700 • to carry the Warning Card with them.
- 701 • how to identify a hypersensitivity reaction [*see Warnings and Precautions (5.1), Medication*
- 702 *Guide*].
- 703 • that if they develop symptoms consistent with a hypersensitivity reaction they should call
- 704 their healthcare provider right away to determine if they should stop taking ZIAGEN.
- 705 • that a hypersensitivity reaction can worsen and lead to hospitalization or death if ZIAGEN is
- 706 not immediately discontinued.
- 707 • that in one trial, more severe hypersensitivity reactions were seen when ZIAGEN was dosed
- 708 600 mg once daily.
- 709 • to not restart ZIAGEN or any other abacavir-containing product following a hypersensitivity
- 710 reaction because more severe symptoms can occur within hours and may include
- 711 life-threatening hypotension and death.
- 712 • that a hypersensitivity reaction is usually reversible if it is detected promptly and ZIAGEN
- 713 is stopped right away.
- 714 • that if they have interrupted ZIAGEN for reasons other than symptoms of hypersensitivity
- 715 (for example, those who have an interruption in drug supply), a serious or fatal
- 716 hypersensitivity reaction may occur with reintroduction of abacavir.
- 717 • to not restart ZIAGEN or any other abacavir-containing product without medical
- 718 consultation and that restarting abacavir needs to be undertaken only if medical care can be
- 719 readily accessed by the patient or others.
- 720 • ZIAGEN should not be coadministered with EPZICOM[®] (abacavir sulfate and lamivudine)
- 721 tablets or TRIZIVIR[®] (abacavir sulfate, lamivudine, and zidovudine) tablets.

722 Lactic Acidosis/Hepatomegaly

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

726 Redistribution/Accumulation of Body Fat

727 Inform patients that redistribution or accumulation of body fat may occur in patients receiving
728 antiretroviral therapy and that the cause and long-term health effects of these conditions are not
729 known at this time [*see Warnings and Precautions (5.4)*].

730 Information About HIV-1 Infection

731 ZIAGEN is not a cure for HIV-1 infection and patients may continue to experience illnesses
732 associated with HIV-1 infection, including opportunistic infections. Patients must remain on
733 continuous HIV therapy to control HIV-1 infection and decrease HIV-related illness. Patients

734 should be told that sustained decreases in plasma HIV-1 RNA have been associated with a
735 reduced risk of progression to AIDS and death. Patients should remain under the care of a
736 physician when using ZIAGEN.

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

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

- 739
- **Do not re-use or share needles or other injection equipment.**
 - **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
 - Continue to practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.
 - Female patients should be advised not to breastfeed. Mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

746

747 COMBIVIR, EPIVIR, EPZICOM, TRIZIVIR, and ZIAGEN are registered trademarks of the
748 ViiV Healthcare group of companies.

749 The other brands listed are trademarks of their respective owners and are not trademarks of the
750 ViiV Healthcare group of companies. The makers of these brands are not affiliated with and do
751 not endorse the ViiV Healthcare group of companies or its products.

752

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754 Manufactured for:



755

756 ViiV Healthcare

757 Research Triangle Park, NC 27709

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759 by:



760

761 GlaxoSmithKline

762 Research Triangle Park, NC 27709

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764 ZGN:XPI

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MEDICATION GUIDE

ZIAGEN® (ZY-uh-jen)

(abacavir sulfate)

tablets and oral solution

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

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

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

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

	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

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

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

795 it again. Taking ZIAGEN again can cause a serious allergic or life-threatening
796 reaction, even if you never had an allergic reaction to it before.

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

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

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

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

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

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

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

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

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 **Who should not take ZIAGEN?**

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

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

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

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

- 848 • **have been tested and know whether or not you have a particular gene**
849 **variation called HLA-B*5701.**
- 850 • **have hepatitis B virus infection or have other liver problems.**
- 851 • **have heart problems, smoke, or have diseases that increase your risk**
852 **of heart disease such as high blood pressure, high cholesterol, or**
853 **diabetes.**
- 854 • **are pregnant or plan to become pregnant.** Taking ZIAGEN during pregnancy
855 has not been associated with an increased risk of birth defects. Talk to your
856 healthcare provider if you are pregnant or plan to become pregnant.
857 **Pregnancy Registry.** If you take ZIAGEN while you are pregnant, talk to your
858 healthcare provider about how you can take part in the Pregnancy Registry for
859 ZIAGEN. The purpose of the pregnancy registry is to collect information about
860 the health of you and your baby.

- 861 • are breastfeeding or plan to breastfeed. **Do not breastfeed if you take**
862 **ZIAGEN.**
- 863 • You should not breastfeed if you have HIV-1 because of the risk of passing
864 HIV-1 to your baby.

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

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

- 868 • alcohol
- 869 • methadone
- 870 • TRIZIVIR (abacavir sulfate, lamivudine, and zidovudine)
- 871 • EPZICOM (abacavir sulfate and lamivudine)

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

874 ZIAGEN may affect the way other medicines work, and other medicines may affect
875 how ZIAGEN works.

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

878 **How should I take ZIAGEN?**

- 879 • **Take ZIAGEN exactly as your healthcare provider tells you to take it.**
- 880 • **ZIAGEN is taken by mouth as a tablet or a strawberry- and banana-**
881 **flavored liquid.**

882 • ZIAGEN may be taken with or without food.

883 • Do not skip doses.

884 • Children aged 3 months and older can also take ZIAGEN. The child's healthcare
885 provider will decide the right dose and whether the child should take the tablet
886 or liquid, based on the child's weight. The dose should not be more than the
887 recommended adult dose.

888 • **Do not let your ZIAGEN run out.**

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

893 **What are the possible side effects of ZIAGEN?**

894 • **ZIAGEN can cause serious side effects including allergic reactions, lactic**
895 **acidosis, and liver problems. See “What is the most important**
896 **information I should know about ZIAGEN?”**

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

901 • **Changes in body fat (fat redistribution).** Changes in body fat (lipoatrophy or
902 lipodystrophy) can happen in some people taking antiretroviral medicines
903 including ZIAGEN.

904 These changes may include:

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

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

908 • **Heart attack (myocardial infarction).** Some HIV medicines including ZIAGEN
909 may increase your risk of heart attack.

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

911 • bad dreams or sleep problems

912 • nausea

913 • headache

914 • tiredness

915 • vomiting

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

917 • fever and chills

918 • nausea

919 • vomiting

920 • rash

921 • ear, nose, or throat infections

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

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

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

928 **How should I store ZIAGEN?**

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

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

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

- 934 • **Do not re-use or share needles or other injection equipment.**
- 935 • **Do not share personal items that can have blood or body fluids on**
936 **them, like toothbrushes and razor blades.**
- 937 • **Do not have any kind of sex without protection.** Always practice safe sex
938 by using a latex or polyurethane condom to lower the chance of sexual contact
939 with any body fluids such as semen, vaginal secretions, or blood.

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

944 This Medication Guide summarizes the most important information about ZIAGEN.
945 If you would like more information, talk with your healthcare provider. You can ask
946 your healthcare provider or pharmacist for the information that is written for
947 healthcare professionals.

948 For more information go to www.ZIAGEN.com or call 1-877-844-8872.

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

950 **Tablets**

951 Active ingredient: abacavir sulfate

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

955 **Oral Solution**

956 Active ingredient: abacavir sulfate

957 Inactive ingredients: artificial strawberry and banana flavors, citric acid
958 (anhydrous), methylparaben and propylparaben (added as preservatives),

959 propylene glycol, saccharin sodium, sodium citrate (dihydrate), sorbitol solution,
960 and water.

961

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

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964 group of companies.

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967 Manufactured for:



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969 ViiV Healthcare

970 Research Triangle Park, NC 27709

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972 by:



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974 GlaxoSmithKline

975 Research Triangle Park, NC 27709

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