

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

Dosage and Administration, Pediatric Patients (2.2)	03/2015
Warnings and Precautions, Use with Other Abacavir-containing Products (5.6)	03/2015

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: Administered either once or twice daily. Dose should be calculated on body weight (kg) and should not exceed 600 mg daily. (2.2)
- Patients with Hepatic Impairment: Mild hepatic impairment – 200 mg twice daily; moderate/severe hepatic impairment – contraindicated. (2.3)

FULL PRESCRIBING INFORMATION: CONTENTS*

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DOSAGE FORMS AND STRENGTHS

- Tablets: 300 mg 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)
- Administration of ZIAGEN with other products containing abacavir is not recommended. (5.6)

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. (6.2)

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: 03/2015

7.2 Methadone

8 USE IN SPECIFIC POPULATIONS

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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 (including EPZICOM[®],
40 TRIUMEQ[®], and TRIZIVIR[®]) in order to avoid reintroduction in a patient with a history of
41 hypersensitivity to abacavir [*see Warnings and 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 or 16 mg per kg once-daily (up to a maximum of
52 600 mg daily) in 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 Scored Tablets in Pediatric Patients**

Weight (kg)	Once-daily Dosing Regimen ^a	Twice-daily Dosing Regimen		
		AM Dose	PM Dose	Total Daily Dose
14 to <20	1 tablet (300 mg)	½ tablet (150 mg)	½ tablet (150 mg)	300 mg
≥20 to <25	1½ tablets (450 mg)	½ tablet (150 mg)	1 tablet (300 mg)	450 mg
≥25	2 tablets (600 mg)	1 tablet (300 mg)	1 tablet (300 mg)	600 mg

60 ^a Data regarding the efficacy of once-daily dosing is limited to subjects who transitioned from
 61 twice-daily dosing to once daily dosing after 36 weeks of treatment [see *Clinical Studies (14.2)*].

62 **2.3 Patients with Hepatic Impairment**

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

68 **3 DOSAGE FORMS AND STRENGTHS**

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

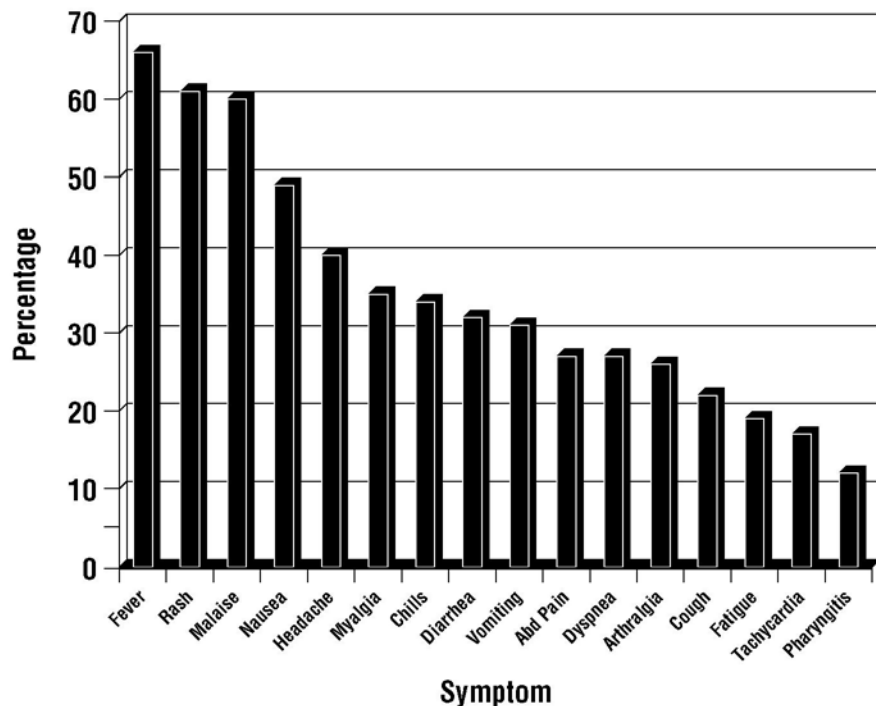
103 Group 4: Constitutional (including generalized malaise, fatigue, or achiness)

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 **5.6 Use with Other Abacavir-containing Products**

217 ZIAGEN is one of multiple abacavir-containing products. Concomitant administration of
218 ZIAGEN with other products containing abacavir is not recommended.

219 **6 ADVERSE REACTIONS**

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

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

229 **6.1 Clinical Trials Experience in Adult Subjects**

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

233 Therapy-naïve Adults

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

239 **Table 2. Treatment-emergent (All Causality) Adverse Reactions of at Least Moderate**
 240 **Intensity (Grades 2-4, Greater than or Equal to 5% Frequency) in Therapy-naive Adults**
 241 **(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%

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

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

247 Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe)
 248 with a greater than or equal to 5% frequency during therapy with ZIAGEN 300 mg twice daily,
 249 lamivudine 150 mg twice daily, and zidovudine 300 mg twice daily compared with indinavir
 250 800 mg 3 times daily, lamivudine 150 mg twice daily, and zidovudine 300 mg twice daily from
 251 CNA3005 are listed in Table 3.

252 **Table 3. Treatment-emergent (All Causality) Adverse Reactions of at Least Moderate**
 253 **Intensity (Grades 2-4, Greater than or Equal to 5% Frequency) in Therapy-naive Adults**
 254 **(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%

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

258 *ZIAGEN Once Daily versus ZIAGEN Twice Daily (CNA30021):* Treatment-emergent
 259 clinical adverse reactions (rated by the investigator as at least moderate) with a greater than or
 260 equal to 5% frequency during therapy with ZIAGEN 600 mg once daily or ZIAGEN 300 mg
 261 twice daily, both in combination with lamivudine 300 mg once daily and efavirenz 600 mg once
 262 daily from CNA30021, were similar. For hypersensitivity reactions, subjects receiving ZIAGEN
 263 once daily showed a rate of 9% in comparison with a rate of 7% for subjects receiving ZIAGEN
 264 twice daily. However, subjects receiving ZIAGEN 600 mg once daily experienced a significantly
 265 higher incidence of severe drug hypersensitivity reactions and severe diarrhea compared with
 266 subjects who received ZIAGEN 300 mg twice daily. Five percent (5%) of subjects receiving
 267 ZIAGEN 600 mg once daily had severe drug hypersensitivity reactions compared with 2% of
 268 subjects receiving ZIAGEN 300 mg twice daily. Two percent (2%) of subjects receiving
 269 ZIAGEN 600 mg once daily had severe diarrhea while none of the subjects receiving ZIAGEN
 270 300 mg twice daily had this event.

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

273 600 mg daily compared with zidovudine 300 mg twice daily, lamivudine 150 mg twice daily,
 274 and efavirenz 600 mg daily from CNA30024 are listed in Table 4.

275 **Table 4. Laboratory Abnormalities (Grades 3-4) in Therapy-naive Adults (CNA30024)**
 276 **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%

277 ULN = Upper limit of normal.

278 n = Number of subjects assessed.

279 Laboratory abnormalities in CNA3005 are listed in Table 5.

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

Grade 3/4 Laboratory Abnormalities	Number of Subjects by Treatment Group	
	ZIAGEN plus Lamivudine/Zidovudine (n = 262)	Indinavir plus Lamivudine/Zidovudine (n = 264)
Elevated CPK (>4 x ULN)	18 (7%)	18 (7%)
ALT (>5.0 x ULN)	16 (6%)	16 (6%)
Neutropenia (<750/mm 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%)

281 ULN = Upper limit of normal.

282 n = Number of subjects assessed.

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

285 **6.2 Clinical Trials Experience in Pediatric Subjects**

286 Therapy-experienced Pediatric Subjects (Twice-daily Dosing)

287 Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe)
288 with a greater than or equal to 5% frequency during therapy with ZIAGEN 8 mg per kg twice
289 daily, lamivudine 4 mg per kg twice daily, and zidovudine 180 mg per m² twice daily compared
290 with lamivudine 4 mg per kg twice daily and zidovudine 180 mg per m² twice daily from
291 CNA3006 are listed in Table 6.

292 **Table 6. Treatment-emergent (All Causality) Adverse Reactions of at Least Moderate**
293 **Intensity (Grades 2-4, Greater than or Equal to 5% Frequency) in Therapy-experienced**
294 **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%

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

300 Other Adverse Events

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

304 *Pediatric Subjects Once-daily vs Twice-daily Dosing (COL105677):* The safety of once-
305 daily compared with twice-daily dosing of ZIAGEN was assessed in the ARROW trial. Primary
306 safety assessment in the ARROW trial was based on Grade 3 and Grade 4 adverse events. The
307 frequency of Grade 3 and 4 adverse events was similar among subjects randomized to once-daily
308 dosing compared with subjects randomized to twice-daily dosing. One event of Grade 4 hepatitis
309 in the once-daily cohort was considered as uncertain causality by the investigator and all other
310 Grade 3 or 4 adverse events were considered not related by the investigator.

311 **6.3 Postmarketing Experience**

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

317 Body as a Whole

318 Redistribution/accumulation of body fat.

319 Cardiovascular

320 Myocardial infarction.

321 Hepatic

322 Lactic acidosis and hepatic steatosis.

323 Skin

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

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

331 **7 DRUG INTERACTIONS**

332 **7.1 Ethanol**

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

336 **7.2 Methadone**

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

343 **8 USE IN SPECIFIC POPULATIONS**

344 **8.1 Pregnancy**

345 Pregnancy Exposure Registry

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

349 Risk Summary

350 Available data from the Antiretroviral Pregnancy Registry show no difference in the risk of
351 overall major birth defects for abacavir compared with the background rate for major birth
352 defects of 2.7% in the US reference population of the Metropolitan Atlanta Congenital Defects
353 Program (MACDP). Abacavir produced fetal malformations and other embryonic and fetal
354 toxicities in rats at 35 times the human exposure at the recommended clinical dose. The
355 relevance of animal findings to human pregnancy registry data is not known.

356 Data

357 *Human Data:* Based on prospective reports from the Antiretroviral Pregnancy Registry of over
358 2,000 exposures to abacavir during pregnancy resulting in live births (including over 900
359 exposed in the first trimester), there was no difference between abacavir and overall birth defects
360 compared with the background birth defect rate of 2.7% in the US reference population of the
361 MACDP. The prevalence of defects in the first trimester was 3.0% (95% CI: 2.0% to 4.4%).

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

371 **8.2 Lactation**

372 Risk Summary

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

377 **8.4 Pediatric Use**

378 The safety and effectiveness of ZIAGEN have been established in pediatric patients aged
379 3 months and older. Use of ZIAGEN is supported by pharmacokinetic trials and evidence from
380 adequate and well-controlled trials of ZIAGEN in adults and pediatric subjects [see *Dosage and*
381 *Administration (2.2), Adverse Reactions (6.2), Clinical Pharmacology (12.3), Clinical Studies*
382 *(14.2)*].

383 **8.5 Geriatric Use**

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

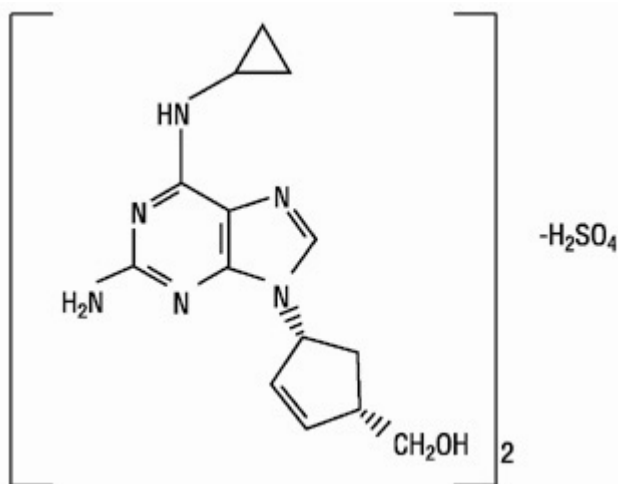
388 **10 OVERDOSAGE**

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

391 **11 DESCRIPTION**

392 ZIAGEN is the brand name for abacavir sulfate, a synthetic carbocyclic nucleoside analogue
393 with inhibitory activity against HIV-1. The chemical name of abacavir sulfate is (1*S*,*cis*)-4-[2-
394 amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1).
395 Abacavir sulfate is the enantiomer with 1*S*, 4*R* absolute configuration on the cyclopentene ring.
396 It has a molecular formula of (C₁₄H₁₈N₆O)₂•H₂SO₄ and a molecular weight of 670.76 daltons. It
397 has the following structural formula:

398



399

400

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

404 ZIAGEN tablets are for oral administration. Each tablet contains abacavir sulfate equivalent to
405 300 mg of abacavir as active ingredient and the following inactive ingredients: colloidal silicon
406 dioxide, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The tablets
407 are coated with a film that is made of hypromellose, polysorbate 80, synthetic yellow iron oxide,
408 titanium dioxide, and triacetin.

409 ZIAGEN oral solution is for oral administration. Each milliliter (1 mL) of ZIAGEN oral solution
410 contains abacavir sulfate equivalent to 20 mg of abacavir (i.e., 20 mg per mL) as active
411 ingredient and the following inactive ingredients: artificial strawberry and banana flavors, citric
412 acid (anhydrous), methylparaben and propylparaben (added as preservatives), propylene glycol,
413 saccharin sodium, sodium citrate (dihydrate), sorbitol solution, and water.

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

416 **12 CLINICAL PHARMACOLOGY**

417 **12.1 Mechanism of Action**

418 Abacavir is an antiviral agent [*see Microbiology (12.4)*].

419 **12.3 Pharmacokinetics**

420 Pharmacokinetics in Adults

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

425 *Absorption and Bioavailability:* Abacavir was rapidly and extensively absorbed after oral
426 administration. The geometric mean absolute bioavailability of the tablet was 83%. Plasma
427 abacavir AUC was similar following administration of the oral solution or tablets. After oral
428 administration of 300 mg twice daily in 20 subjects, the steady-state peak serum abacavir
429 concentration (C_{\max}) was 3.0 ± 0.89 mcg per mL (mean \pm SD) and $AUC_{(0-12\text{ h})}$ was
430 6.02 ± 1.73 mcg•hour per mL. After oral administration of a single dose of 600 mg of abacavir in
431 20 subjects, C_{\max} was 4.26 ± 1.19 mcg per mL (mean \pm SD) and AUC_{∞} was
432 11.95 ± 2.51 mcg•hour per mL.

433 *Distribution:* The apparent volume of distribution after IV administration of abacavir was
434 0.86 ± 0.15 L per kg, suggesting that abacavir distributes into extravascular space. In 3 subjects,
435 the CSF $AUC_{(0-6\text{ h})}$ to plasma abacavir $AUC_{(0-6\text{ h})}$ ratio ranged from 27% to 33%.

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

440 *Metabolism:* In humans, abacavir is not significantly metabolized by cytochrome P450
441 enzymes. The primary routes of elimination of abacavir are metabolism by alcohol
442 dehydrogenase (to form the 5'-carboxylic acid) and glucuronyl transferase (to form the
443 5'-glucuronide). The metabolites do not have antiviral activity. In vitro experiments reveal that
444 abacavir does not inhibit human CYP3A4, CYP2D6, or CYP2C9 activity at clinically relevant
445 concentrations.

446 *Elimination:* Elimination of abacavir was quantified in a mass balance trial following
447 administration of a 600-mg dose of ¹⁴C-abacavir: 99% of the radioactivity was recovered, 1.2%
448 was excreted in the urine as abacavir, 30% as the 5'-carboxylic acid metabolite, 36% as the
449 5'-glucuronide metabolite, and 15% as unidentified minor metabolites in the urine. Fecal
450 elimination accounted for 16% of the dose.

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

453 Effects of Food on Oral Absorption

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

459 Special Populations

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

463 *Hepatic Impairment:* The pharmacokinetics of abacavir have been studied in subjects with mild
464 hepatic impairment (Child-Pugh score 5 to 6). Results showed that there was a mean increase of
465 89% in the abacavir AUC and an increase of 58% in the half-life of abacavir after a single dose
466 of 600 mg of abacavir. The AUCs of the metabolites were not modified by mild liver disease;
467 however, the rates of formation and elimination of the metabolites were decreased. A dose of
468 200 mg (provided by 10 mL of ZIAGEN oral solution) administered twice daily is recommended
469 for patients with mild liver disease. The safety, efficacy, and pharmacokinetics of abacavir have
470 not been studied in subjects with moderate or severe hepatic impairment; therefore, ZIAGEN is
471 contraindicated in these patients.

472 *Pediatric Patients:* The pharmacokinetics of abacavir have been studied after either single or
473 repeat doses of ZIAGEN in 169 pediatric subjects. Subjects receiving abacavir oral solution
474 according to the recommended dosage regimen achieved plasma concentrations of abacavir
475 similar to adults. Subjects receiving abacavir oral tablets achieved higher plasma concentrations
476 of abacavir than subjects receiving oral solution.

477 The pharmacokinetics of abacavir dosed once daily in HIV-1-infected pediatric subjects aged
478 3 months through 12 years was evaluated in 3 trials (PENTA 13 [n = 14], PENTA 15 [n = 18],
479 and ARROW [n = 36]). All 3 trials were 2-period, crossover, open-label pharmacokinetic trials
480 of twice- versus once-daily dosing of abacavir and lamivudine. For the oral solution as well as
481 the tablet formulation, these 3 trials demonstrated that once-daily dosing provides comparable
482 AUC₀₋₂₄ to twice-daily dosing of abacavir at the same total daily dose. The mean C_{max} was
483 approximately 1.6- to 2.3-fold higher with abacavir once-daily dosing compared with twice-daily
484 dosing.

485 *Geriatric Patients:* The pharmacokinetics of ZIAGEN have not been studied in subjects over
486 65 years of age.

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

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

492 Drug Interactions

493 In human liver microsomes, abacavir did not inhibit cytochrome P450 isoforms (2C9, 2D6,
494 3A4). Based on these data, it is unlikely that clinically significant drug interactions will occur
495 between abacavir and drugs metabolized through these pathways.

496 *Lamivudine and/or Zidovudine:* Due to the common metabolic pathways of abacavir and
497 zidovudine via glucuronyl transferase, 15 HIV-1-infected subjects were enrolled in a crossover
498 trial evaluating single doses of abacavir (600 mg), lamivudine (150 mg), and zidovudine
499 (300 mg) alone or in combination. Analysis showed no clinically relevant changes in the
500 pharmacokinetics of abacavir with the addition of lamivudine or zidovudine or the combination
501 of lamivudine and zidovudine. Lamivudine exposure (AUC decreased 15%) and zidovudine
502 exposure (AUC increased 10%) did not show clinically relevant changes with concurrent
503 abacavir.

504 *Ethanol:* Due to the common metabolic pathways of abacavir and ethanol via alcohol
505 dehydrogenase, the pharmacokinetic interaction between abacavir and ethanol was studied in
506 24 HIV-1-infected male subjects. Each subject received the following treatments on separate
507 occasions: a single 600-mg dose of abacavir, 0.7 g per kg ethanol (equivalent to 5 alcoholic
508 drinks), and abacavir 600 mg plus 0.7 g per kg ethanol. Coadministration of ethanol and abacavir

509 resulted in a 41% increase in abacavir AUC_{∞} and a 26% increase in abacavir $t_{1/2}$. In males,
510 abacavir had no effect on the pharmacokinetic properties of ethanol, so no clinically significant
511 interaction is expected in men. This interaction has not been studied in females.

512 **Methadone:** In a trial of 11 HIV-1-infected subjects receiving methadone-maintenance therapy
513 (40 mg and 90 mg daily), with 600 mg of ZIAGEN twice daily (twice the currently
514 recommended dose), oral methadone clearance increased 22% (90% CI: 6% to 42%). This
515 alteration will not result in a methadone dose modification in the majority of patients; however,
516 an increased methadone dose may be required in a small number of patients. The addition of
517 methadone had no clinically significant effect on the pharmacokinetic properties of abacavir.

518 **12.4 Microbiology**

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

527 Antiviral Activity

528 The antiviral activity of abacavir against HIV-1 was evaluated against a T-cell tropic laboratory
529 strain HIV-1_{IIB} in lymphoblastic cell lines, a monocyte/macrophage tropic laboratory strain
530 HIV-1_{BaL} in primary monocytes/macrophages, and clinical isolates in peripheral blood
531 mononuclear cells. The concentration of drug necessary to effect viral replication by 50 percent
532 (EC_{50}) ranged from 3.7 to 5.8 μM (1 μM = 0.28 mcg per mL) and 0.07 to 1.0 μM against
533 HIV-1_{IIB} and HIV-1_{BaL}, respectively, and was $0.26 \pm 0.18 \mu\text{M}$ against 8 clinical isolates. The
534 EC_{50} values of abacavir against different HIV-1 clades (A-G) ranged from 0.0015 to 1.05 μM ,
535 and against HIV-2 isolates, from 0.024 to 0.49 μM . The antiviral activity of abacavir in cell
536 culture was not antagonized when combined with the nucleoside reverse transcriptase inhibitors
537 (NRTIs) didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine or zidovudine,
538 the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, or the protease inhibitor
539 (PI) amprenavir. Ribavirin (50 μM) had no effect on the anti-HIV-1 activity of abacavir in cell
540 culture.

541 Resistance

542 HIV-1 isolates with reduced susceptibility to abacavir have been selected in cell culture and were
543 also obtained from subjects treated with abacavir. Genotypic analysis of isolates selected in cell
544 culture and recovered from abacavir-treated subjects demonstrated that amino acid substitutions
545 K65R, L74V, Y115F, and M184V/I in RT contributed to abacavir resistance. In a trial of

546 therapy-naive adults receiving ZIAGEN 600 mg once daily (n = 384) or 300 mg twice daily
547 (n = 386), in a background regimen of lamivudine 300 mg once daily and efavirenz 600 mg once
548 daily (CNA30021), the incidence of virologic failure at 48 weeks was similar between the 2
549 groups (11% in both arms). Genotypic (n = 38) and phenotypic analyses (n = 35) of virologic
550 failure isolates from this trial showed that the RT substitutions that emerged during abacavir
551 once-daily and twice-daily therapy were K65R, L74V, Y115F, and M184V/I. The substitution
552 M184V/I was the most commonly observed substitution in virologic failure isolates from
553 subjects receiving abacavir once daily (56%, 10 of 18) and twice daily (40%, 8 of 20).

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

558 Cross-resistance:

559 Cross-resistance has been observed among NRTIs. Isolates containing abacavir
560 resistance-associated substitutions, namely, K65R, L74V, Y115F, and M184V, exhibited
561 cross-resistance to didanosine, emtricitabine, lamivudine, tenofovir, and zalcitabine in cell
562 culture and in subjects. The K65R substitution can confer resistance to abacavir, didanosine,
563 emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine; the L74V substitution can confer
564 resistance to abacavir, didanosine, and zalcitabine; and the M184V substitution can confer
565 resistance to abacavir, didanosine, emtricitabine, lamivudine, and zalcitabine. An increasing
566 number of thymidine analogue mutations (TAMs: M41L, D67N, K70R, L210W, T215Y/F,
567 K219E/R/H/Q/N) is associated with a progressive reduction in abacavir susceptibility.

568 **13 NONCLINICAL TOXICOLOGY**

569 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

570 Carcinogenicity

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

579 Mutagenicity

580 Abacavir induced chromosomal aberrations both in the presence and absence of metabolic
581 activation in an in vitro cytogenetic study in human lymphocytes. Abacavir was mutagenic in the

582 absence of metabolic activation, although it was not mutagenic in the presence of metabolic
583 activation in an L5178Y mouse lymphoma assay. Abacavir was clastogenic in males and not
584 clastogenic in females in an in vivo mouse bone marrow micronucleus assay.

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

587 Impairment of Fertility

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

591 **13.2 Animal Toxicology and/or Pharmacology**

592 Myocardial degeneration was found in mice and rats following administration of abacavir for
593 2 years. The systemic exposures were equivalent to 7 to 24 times the expected systemic exposure
594 in humans. The clinical relevance of this finding has not been determined.

595 **14 CLINICAL STUDIES**

596 **14.1 Adult Trials**

597 Therapy-naive Adults

598 CNA30024 was a multicenter, double-blind, controlled trial in which 649 HIV-1-infected,
599 therapy-naive adults were randomized and received either ZIAGEN (300 mg twice daily),
600 lamivudine (150 mg twice daily), and efavirenz (600 mg once daily); or zidovudine (300 mg
601 twice daily), lamivudine (150 mg twice daily), and efavirenz (600 mg once daily). The duration
602 of double-blind treatment was at least 48 weeks. Trial participants were male (81%), white
603 (51%), black (21%), and Hispanic (26%). The median age was 35 years; the median pretreatment
604 CD4+ cell count was 264 cells per mm³, and median plasma HIV-1 RNA was 4.79 log₁₀ copies
605 per mL. The outcomes of randomized treatment are provided in Table 7.

606 **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%

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

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

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

614 After 48 weeks of therapy, the median CD4+ cell count increases from baseline were
 615 209 cells per mm³ in the group receiving ZIAGEN and 155 cells per mm³ in the zidovudine
 616 group. Through Week 48, 8 subjects (2%) in the group receiving ZIAGEN (5 CDC
 617 classification C events and 3 deaths) and 5 subjects (2%) on the zidovudine arm (3 CDC
 618 classification C events and 2 deaths) experienced clinical disease progression.

619 CNA3005 was a multicenter, double-blind, controlled trial in which 562 HIV-1-infected,
 620 therapy-naive adults were randomized to receive either ZIAGEN (300 mg twice daily) plus
 621 COMBIVIR[®] (lamivudine 150 mg/zidovudine 300 mg twice daily), or indinavir (800 mg 3 times
 622 a day) plus COMBIVIR twice daily. The trial was stratified at randomization by pre-entry
 623 plasma HIV-1 RNA 10,000 to 100,000 copies per mL and plasma HIV-1 RNA greater than
 624 100,000 copies per mL. Trial participants were male (87%), white (73%), black (15%), and
 625 Hispanic (9%). At baseline the median age was 36 years; the median baseline CD4+ cell count
 626 was 360 cells per mm³, and median baseline plasma HIV-1 RNA was 4.8 log₁₀ copies per mL.
 627 Proportions of subjects with plasma HIV-1 RNA less than 400 copies per mL (using Roche
 628 AMPLICOR HIV-1 MONITOR Test) through 48 weeks of treatment are summarized in Table 8.

629 **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%

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

631 ^b Includes viral rebound and failure to achieve confirmed less than 400 copies per mL by Week
632 48.

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

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

636 **Table 9. Proportions of Responders through Week 48 by Screening Plasma HIV-1 RNA
637 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

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

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

646 CNA30021 was an international, multicenter, double-blind, controlled trial in which
647 770 HIV-1-infected, therapy-naive adults were randomized and received either abacavir 600 mg
648 once daily or abacavir 300 mg twice daily, both in combination with lamivudine 300 mg once
649 daily and efavirenz 600 mg once daily. The double-blind treatment duration was at least
650 48 weeks. Trial participants had a mean age of 37 years; were male (81%), white (54%), black
651 (27%), and American Hispanic (15%). The median baseline CD4+ cell count was 262 cells per
652 mm³ (range: 21 to 918 cells per mm³) and the median baseline plasma HIV-1 RNA was
653 4.89 log₁₀ copies per mL (range: 2.60 to 6.99 log₁₀ copies per mL).

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

655 **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%

656 ^a Subjects achieved and maintained confirmed HIV-1 RNA less than 50 copies per mL (less than
657 400 copies per mL) through Week 48 (Roche AMPLICOR Ultrasensitive HIV-1 MONITOR
658 standard test version 1.0).

659 ^b Includes viral rebound, failure to achieve confirmed less than 50 copies per mL (less than
660 400 copies per mL) by Week 48, and insufficient viral load response.

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

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

669 **14.2 Pediatric Trials**

670 Therapy-experienced Pediatric Subjects

671 CNA3006 was a randomized, double-blind trial comparing ZIAGEN 8 mg per kg twice daily
672 plus lamivudine 4 mg per kg twice daily plus zidovudine 180 mg per m² twice daily versus
673 lamivudine 4 mg per kg twice daily plus zidovudine 180 mg per m² twice daily. Two hundred
674 and five therapy-experienced pediatric subjects were enrolled: female (56%), white (17%), black
675 (50%), Hispanic (30%), median age of 5.4 years, baseline CD4+ cell percent greater than 15%
676 (median = 27%), and median baseline plasma HIV-1 RNA of 4.6 log₁₀ copies per mL. Eighty
677 percent and 55% of subjects had prior therapy with zidovudine and lamivudine, respectively,
678 most often in combination. The median duration of prior nucleoside analogue therapy was
679 2 years. At 16 weeks the proportion of subjects responding based on plasma HIV-1 RNA less
680 than or equal to 400 copies per mL was significantly higher in subjects receiving ZIAGEN plus
681 lamivudine plus zidovudine compared with subjects receiving lamivudine plus zidovudine, 13%
682 versus 2%, respectively. Median plasma HIV-1 RNA changes from baseline were -0.53 log₁₀
683 copies per mL in the group receiving ZIAGEN plus lamivudine plus zidovudine compared with -

684 0.21 log₁₀ copies per mL in the group receiving lamivudine plus zidovudine. Median CD4+ cell
 685 count increases from baseline were 69 cells per mm³ in the group receiving ZIAGEN plus
 686 lamivudine plus zidovudine and 9 cells per mm³ in the group receiving lamivudine plus
 687 zidovudine.

688 Once-daily Dosing

689 ARROW (COL105677) was a 5-year randomized, multicenter trial which evaluated multiple
 690 aspects of clinical management of HIV-1 infection in pediatric subjects. HIV-1–infected,
 691 treatment-naïve subjects aged 3 months to 17 years were enrolled and treated with a first-line
 692 regimen containing ZIAGEN and lamivudine, dosed twice daily according to World Health
 693 Organization recommendations. After a minimum of 36 weeks of treatment, subjects were given
 694 the option to participate in Randomization 3 of the ARROW trial, comparing the safety and
 695 efficacy of once-daily dosing with twice-daily dosing of ZIAGEN and lamivudine, in
 696 combination with a third antiretroviral drug, for an additional 96 weeks. Of the 1,206 original
 697 ARROW subjects, 669 participated in Randomization 3. Virologic suppression was not a
 698 requirement for participation at baseline for Randomization 3 (following a minimum of 36 weeks
 699 of twice-daily treatment), 75% of subjects in the twice-daily cohort were virologically
 700 suppressed compared with 71% of subjects in the once-daily cohort.

701 The proportions of subjects with HIV-1 RNA less than 80 copies per mL through 96 weeks are
 702 shown in Table 11. The differences between virologic responses in the two treatment arms were
 703 comparable across baseline characteristics for gender and age.

704 **Table 11. Virologic Outcome of Randomized Treatment at Week 96^a (ARROW**
 705 **Randomization 3)**

Outcome	ZIAGEN plus Lamivudine Twice-daily Dosing (n = 333)	ZIAGEN plus Lamivudine Once-daily Dosing (n = 336)
HIV-1 RNA <80 copies/mL ^b	70%	67%
HIV-1 RNA ≥80 copies/mL ^c	28%	31%
No virologic data		
Discontinued due to adverse event or death	1%	<1%
Discontinued study for other reasons ^d	0%	<1%
Missing data during window but on study	1%	1%

706

- 707 ^a Analyses were based on the last observed viral load data within the Week 96 window.
708 ^b Predicted difference (95% CI) of response rate is -4.5% (-11% to 2%) at Week 96.
709 ^c Includes subjects who discontinued due to lack or loss of efficacy or for reasons other than an
710 adverse event or death, and had a viral load value of greater than or equal to 80 copies per mL, or
711 subjects who had a switch in background regimen that was not permitted by the protocol.
712 ^d Other includes reasons such as withdrew consent, loss to follow-up, etc. and the last available
713 HIV-1 RNA less than 80 copies per mL (or missing).

714 **15 REFERENCES**

- 715 1. Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study Group. *Lancet*.
716 2008;371 (9622):1417-1426.

717 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

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

722 Unit dose blister packs of 60 tablets (NDC 49702-221-44). Each pack contains 6 blister cards of
723 10 tablets each.

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

725 ZIAGEN oral solution is a clear to opalescent, yellowish, strawberry-banana-flavored liquid.
726 Each mL of the solution contains abacavir sulfate equivalent to 20 mg of abacavir. It is packaged
727 in plastic bottles as follows:

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

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

732 **17 PATIENT COUNSELING INFORMATION**

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

734 Hypersensitivity Reaction

735 Inform patients:

- 736 • that a Medication Guide and Warning Card summarizing the symptoms of the abacavir
737 hypersensitivity reaction and other product information will be dispensed by the pharmacist
738 with each new prescription and refill of ZIAGEN, and instruct the patient to read the
739 Medication Guide and Warning Card every time to obtain any new information that may be

740 present about ZIAGEN. The complete text of the Medication Guide is reprinted at the end of
741 this document.

- 742 • to carry the Warning Card with them.
- 743 • how to identify a hypersensitivity reaction [*see Warnings and Precautions (5.1), Medication*
744 *Guide*].
- 745 • that if they develop symptoms consistent with a hypersensitivity reaction they should call
746 their healthcare provider right away to determine if they should stop taking ZIAGEN.
- 747 • that a hypersensitivity reaction can worsen and lead to hospitalization or death if ZIAGEN is
748 not immediately discontinued.
- 749 • that in one trial, more severe hypersensitivity reactions were seen when ZIAGEN was dosed
750 600 mg once daily.
- 751 • to not restart ZIAGEN or any other abacavir-containing product following a hypersensitivity
752 reaction because more severe symptoms can occur within hours and may include
753 life-threatening hypotension and death.
- 754 • that a hypersensitivity reaction is usually reversible if it is detected promptly and ZIAGEN
755 is stopped right away.
- 756 • that if they have interrupted ZIAGEN for reasons other than symptoms of hypersensitivity
757 (for example, those who have an interruption in drug supply), a serious or fatal
758 hypersensitivity reaction may occur with reintroduction of abacavir.
- 759 • to not restart ZIAGEN or any other abacavir-containing product without medical
760 consultation and that restarting abacavir needs to be undertaken only if medical care can be
761 readily accessed by the patient or others.
- 762 • ZIAGEN should not be coadministered with EPZICOM (abacavir sulfate and lamivudine)
763 tablets, TRIUMEQ (abacavir, dolutegravir, and lamivudine) tablets, or TRIZIVIR (abacavir
764 sulfate, lamivudine, and zidovudine) tablets.

765 Lactic Acidosis/Hepatomegaly

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

769 Redistribution/Accumulation of Body Fat

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

773 Information about HIV-1 Infection

774 Inform patients that ZIAGEN is not a cure for HIV-1 infection and patients may continue to
775 experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients
776 must remain on continuous HIV therapy to control HIV-1 infection and decrease HIV-related
777 illness. Patients should be told that sustained decreases in plasma HIV-1 RNA have been
778 associated with a reduced risk of progression to AIDS and death. Patients should remain under
779 the care of a physician when using ZIAGEN.

780 Patients should be informed to take all HIV medications exactly as prescribed. If you miss a dose
781 of ZIAGEN, take it as soon as you remember. Do not take 2 doses at the same time. If you are
782 not sure about your dosing, call your healthcare provider.

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

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

791
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793 trademarks of the ViiV Healthcare group of companies.

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796 not endorse the ViiV Healthcare group of companies or its products.

797

798

799 Manufactured for:



800

801 ViiV Healthcare

802 Research Triangle Park, NC 27709

803

804 by:



805

806 GlaxoSmithKline

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809 ZGN:XPI

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MEDICATION GUIDE

ZIAGEN[®] (ZY-uh-jen) (abacavir sulfate) **tablets and oral solution**

817

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

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

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

829 **If you get a symptom from 2 or more of the following groups while**
830 **taking ZIAGEN, call your healthcare provider right away to find out if**
831 **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

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

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

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

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

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

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

- 854 • you feel very weak or tired
- 855 • you have unusual (not normal) muscle pain
- 856 • you have trouble breathing
- 857 • you have stomach pain with nausea and vomiting
- 858 • you feel cold, especially in your arms and legs
- 859 • you feel dizzy or light-headed

- 860
- you have a fast or irregular heartbeat
- 861 • **Serious liver problems. Some people who have taken medicines like**
862 **ZIAGEN have developed serious liver problems called hepatotoxicity,**
863 **with liver enlargement (hepatomegaly) and fat in the liver (steatosis).**
864 **Hepatomegaly with steatosis is a serious medical emergency that can**
865 **cause death.**

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

- 868
- your skin or the white part of your eyes turns yellow (jaundice)
- 869
- your urine turns dark
- 870
- your bowel movements (stools) turn light in color
- 871
- you don't feel like eating food for several days or longer
- 872
- you feel sick to your stomach (nausea)
- 873
- you have lower stomach area (abdominal) pain

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

877 **What is ZIAGEN?**

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

- 882
- **ZIAGEN does not cure HIV infection or AIDS.**
- 883
- It is not known if ZIAGEN will help you live longer or have fewer of the medical
884 problems that people get with HIV or AIDS.
- 885
- It is very important that you see your doctor regularly while you are taking
886 ZIAGEN.

887 **Who should not take ZIAGEN?**

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

- 889
- **are allergic to abacavir or any of the ingredients in ZIAGEN. See the**
890 **end of this Medication Guide for a complete list of ingredients in**
891 **ZIAGEN.**
- 892
- **have certain liver problems.**

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

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

- 895 • **have been tested and know whether or not you have a particular gene**
896 **variation called HLA-B*5701.**
- 897 • **have hepatitis B virus infection or have other liver problems.**
- 898 • **have heart problems, smoke, or have diseases that increase your risk**
899 **of heart disease such as high blood pressure, high cholesterol, or**
900 **diabetes.**
- 901 • **are pregnant or plan to become pregnant.** Taking ZIAGEN during pregnancy
902 has not been associated with an increased risk of birth defects. Talk to your
903 healthcare provider if you are pregnant or plan to become pregnant.
904 **Pregnancy Registry.** If you take ZIAGEN while you are pregnant, talk to your
905 healthcare provider about how you can take part in the Pregnancy Registry for
906 ZIAGEN. The purpose of the pregnancy registry is to collect information about
907 the health of you and your baby.
- 908 • are breastfeeding or plan to breastfeed. **Do not breastfeed if you take**
909 **ZIAGEN.**
- 910 • You should not breastfeed if you have HIV-1 because of the risk of passing
911 HIV-1 to your baby.

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

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

- 915 • alcohol
- 916 • methadone
- 917 • TRIZIVIR (abacavir sulfate, lamivudine, and zidovudine)
- 918 • EPZICOM (abacavir sulfate and lamivudine)
- 919 • TRIUMEQ (abacavir, dolutegravir, and lamivudine)

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

922 ZIAGEN may affect the way other medicines work, and other medicines may affect
923 how ZIAGEN works.

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

926 **How should I take ZIAGEN?**

- 927 • **Take ZIAGEN exactly as your healthcare provider tells you to take it.**
- 928 • **ZIAGEN is taken by mouth as a tablet or a strawberry- and banana-**
- 929 **flavored liquid.**
- 930 • ZIAGEN may be taken with or without food.
- 931 • Do not skip doses. If you miss a dose of ZIAGEN, take it as soon as you
- 932 remember. Do not take 2 doses at the same time. If you are not sure about
- 933 your dosing, call your healthcare provider.
- 934 • Children aged 3 months and older can also take ZIAGEN. The child's healthcare
- 935 provider will decide the right dose and whether the child should take the tablet
- 936 or liquid, based on the child's weight. The dose should not be more than the
- 937 recommended adult dose.
- 938 • **Do not let your ZIAGEN run out.**
- 939 If you stop your anti-HIV medicines, even for a short time, the amount of virus
- 940 in your blood may increase and the virus may become harder to treat. If you
- 941 take too much ZIAGEN, call your healthcare provider or poison control center or
- 942 go to the nearest hospital emergency room right away.

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

- 944 • **ZIAGEN can cause serious side effects including allergic reactions, lactic**
- 945 **acidosis, and liver problems. See "What is the most important**
- 946 **information I should know about ZIAGEN?"**
- 947 • **Changes in immune system (Immune Reconstitution Syndrome).** Your
- 948 immune system may get stronger and begin to fight infections that have been
- 949 hidden in your body for a long time. Tell your healthcare provider if you start
- 950 having new or worse symptoms of infection after you start taking ZIAGEN.
- 951 • **Changes in body fat (fat redistribution).** Changes in body fat (lipoatrophy or
- 952 lipodystrophy) can happen in some people taking antiretroviral medicines
- 953 including ZIAGEN.
- 954 These changes may include:
- 955 • more fat in or around your trunk, upper back and neck (buffalo hump),
- 956 breast, or chest
- 957 • loss of fat in your legs, arms, or face
- 958 • **Heart attack (myocardial infarction).** Some HIV medicines including ZIAGEN
- 959 may increase your risk of heart attack.

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

961 • bad dreams or sleep problems

962 • nausea

963 • headache

964 • tiredness

965 • vomiting

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

967 • fever and chills

968 • nausea

969 • vomiting

970 • rash

971 • ear, nose, or throat infections

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

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

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

978 **How should I store ZIAGEN?**

979 • Store ZIAGEN at room temperature, between 68°F to 77°F (20°C to 25°C).

980 • Do not freeze ZIAGEN.

981 • **Keep ZIAGEN and all medicines out of the reach of children.**

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

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

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

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

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

990 Medicines are sometimes prescribed for purposes other than those listed in a

991 Medication Guide. Do not use ZIAGEN for a condition for which it was not

992 prescribed. Do not give ZIAGEN to other people, even if they have the same
993 symptoms that you have. It may harm them.

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

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

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

1000 **Tablets**

1001 Active ingredient: abacavir sulfate

1002 Inactive ingredients: colloidal silicon dioxide, magnesium stearate, microcrystalline
1003 cellulose, and sodium starch glycolate, and a film-coating made of hypromellose,
1004 polysorbate 80, synthetic yellow iron oxide, titanium dioxide, and triacetin.

1005 **Oral Solution**

1006 Active ingredient: abacavir sulfate

1007 Inactive ingredients: artificial strawberry and banana flavors, citric acid
1008 (anhydrous), methylparaben and propylparaben (added as preservatives),
1009 propylene glycol, saccharin sodium, sodium citrate (dihydrate), sorbitol solution,
1010 and water.

1011

1012 This Medication Guide has been approved by the US Food and Drug Administration.

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1014 Healthcare group of companies.

1015

1016

1017 Manufactured for:



1018

1019 ViiV Healthcare

1020 Research Triangle Park, NC 27709

1021

1022 by:



1023

1024 GlaxoSmithKline

1025 Research Triangle Park, NC 27709

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1028 March 2015

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