

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 (2)	05/2012
Warnings and Precautions, Hypersensitivity Reaction (5.1)	05/2012
Warnings and Precautions, Immune Reconstitution Syndrome (5.3)	11/2011

INDICATIONS AND USAGE

ZIAGEN, a nucleoside analogue, is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. (1)

DOSAGE AND ADMINISTRATION

- A medication guide and warning card should be dispensed with each new prescription and refill. (2)
- Adults: 600 mg daily, administered as either 300 mg twice daily or 600 mg once daily. (2.1)

- Pediatric Patients Aged 3 Months and Older: Dose should be calculated on body weight (kg) and should not exceed 300 mg twice daily. (2.2)
- Patients With Hepatic Impairment: Mild hepatic impairment – 200 mg twice daily; moderate/severe hepatic impairment – contraindicated. (2.3)

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

- The most commonly reported adverse reactions of at least moderate intensity (incidence $\geq 10\%$) in adult HIV-1 clinical 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 $\geq 5\%$) 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)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 05/2012

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1 **FULL PRESCRIBING INFORMATION**

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

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

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

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

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

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

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

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

33 **1 INDICATIONS AND USAGE**

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

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

38 ZIAGEN is one of multiple products containing abacavir. Before starting ZIAGEN, review
39 medical history for prior exposure to any abacavir-containing product in order to avoid
40 reintroduction in a patient with a history of hypersensitivity to abacavir [*see Warnings and*
41 *Precautions (5.1), Adverse Reactions (6)*].

42 **2 DOSAGE AND ADMINISTRATION**

- 43 • A Medication Guide and Warning Card that provide information about recognition of
44 hypersensitivity reactions should be dispensed with each new prescription and refill.
45
- 46 • ZIAGEN may be taken with or without food.

47 **2.1 Adult Patients**

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

50 **2.2 Pediatric Patients**

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

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

60
61 **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

62 **2.3 Patients With Hepatic Impairment**

63 The recommended dose of ZIAGEN in patients with mild hepatic impairment
64 (Child-Pugh score 5 to 6) is 200 mg twice daily. To enable dose reduction, ZIAGEN Oral
65 Solution (10 mL twice daily) should be used for the treatment of these patients. The safety,
66 efficacy, and pharmacokinetic properties of abacavir have not been established in patients with
67 moderate to severe hepatic impairment; therefore, ZIAGEN is contraindicated in these patients.
68

69 **3 DOSAGE FORMS AND STRENGTHS**

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

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

74 **4 CONTRAINDICATIONS**

75 ZIAGEN is contraindicated in patients with:

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

81 **5 WARNINGS AND PRECAUTIONS**

82 **5.1 Hypersensitivity Reaction**

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

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

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

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

101 Group 1: Fever

102 Group 2: Rash

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

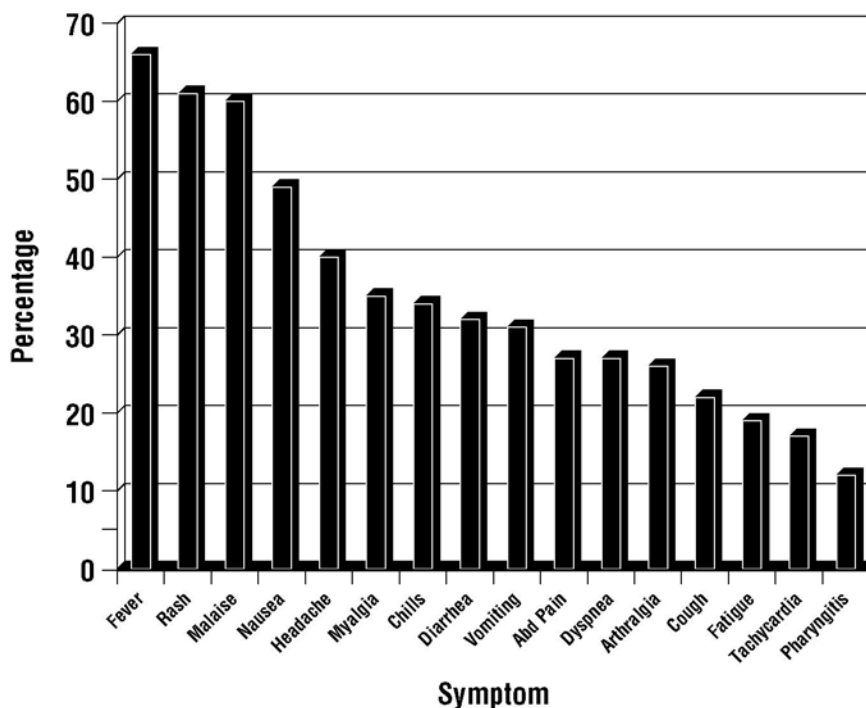
104 Group 4: Constitutional (including generalized malaise, fatigue, or achiness)

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

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

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

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



118
119

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

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

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

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

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

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

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

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

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

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

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

172 regimen is not recommended and should be considered only with close medical supervision and
173 under exceptional circumstances where potential benefit outweighs the risk.

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

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

181 **5.2 Lactic Acidosis/Severe Hepatomegaly With Steatosis**

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

191 **5.3 Immune Reconstitution Syndrome**

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

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

201 **5.4 Fat Redistribution**

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

207 **5.5 Myocardial Infarction**

208 In a published prospective, observational, epidemiological trial designed to investigate
209 the rate of myocardial infarction in patients on combination antiretroviral therapy, the use of
210 abacavir within the previous 6 months was correlated with an increased risk of myocardial
211 infarction (MI).¹ In a sponsor-conducted pooled analysis of clinical trials, no excess risk of

212 myocardial infarction was observed in abacavir-treated subjects as compared with control
213 subjects. In totality, the available data from the observational cohort and from clinical trials are
214 inconclusive.

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

218 **6 ADVERSE REACTIONS**

219 The following adverse reactions are discussed in greater detail in other sections of the
220 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**

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

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

238

239 **Table 2. Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate**
240 **Intensity (Grades 2-4, ≥5% Frequency) in Therapy-Naive Adults (CNA30024^a) Through**
241 **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
244 investigators in 9% of 324 subjects in the abacavir group and 3% of 325 subjects in the
245 zidovudine group.

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

248

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

254

255 **Table 3. Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate**
256 **Intensity (Grades 2-4, ≥5% Frequency) in Therapy-Naive Adults (CNA3005) Through**
257 **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%

258
259 Five subjects receiving ZIAGEN in CNA3005 experienced worsening of pre-existing
260 depression compared with none in the indinavir arm. The background rates of pre-existing
261 depression were similar in the 2 treatment arms.

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

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

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

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

279

280 **Table 4. Laboratory Abnormalities (Grades 3-4) in Therapy-Naive Adults (CNA30024)**
281 **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%

282 ULN = Upper limit of normal.

283 n = Number of subjects assessed.

284

285 Laboratory abnormalities in CNA3005 are listed in Table 5.

286

287 **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%)

288 ULN = Upper limit of normal.

289 n = Number of subjects assessed.

290

291 The frequencies of treatment-emergent laboratory abnormalities were comparable
292 between treatment groups in CNA30021.

293 Pediatric Trials: Therapy-Experienced Pediatric Subjects: Treatment-emergent
294 clinical adverse reactions (rated by the investigator as moderate or severe) with a greater than or
295 equal to 5% frequency during therapy with ZIAGEN 8 mg/kg twice daily, lamivudine 4 mg/kg
296 twice daily, and zidovudine 180 mg/m² twice daily compared with lamivudine 4 mg/kg twice
297 daily and zidovudine 180 mg/m² twice daily from CNA3006 are listed in Table 6.
298

299 **Table 6. Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate**
300 **Intensity (Grades 2-4, ≥5% Frequency) in Therapy-Experienced Pediatric Subjects**
301 **(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%

302
303 Laboratory Abnormalities: In CNA3006, laboratory abnormalities (anemia,
304 neutropenia, liver function test abnormalities, and CPK elevations) were observed with similar
305 frequencies as in a trial of therapy-naïve adults (CNA30024). Mild elevations of blood glucose
306 were more frequent in pediatric subjects receiving ZIAGEN (CNA3006) as compared with adult
307 subjects (CNA30024).

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

311 **6.2 Postmarketing Experience**

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

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

318 Cardiovascular: Myocardial infarction.

319 Hepatic: Lactic acidosis and hepatic steatosis.

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

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

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

327 **7 DRUG INTERACTIONS**

328 **7.1 Ethanol**

329 Abacavir has no effect on the pharmacokinetic properties of ethanol. Ethanol decreases
330 the elimination of abacavir causing an increase in overall exposure [*see Clinical Pharmacology*
331 (12.3)].

332 **7.2 Methadone**

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

339 **8 USE IN SPECIFIC POPULATIONS**

340 **8.1 Pregnancy**

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

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

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

355 **8.3 Nursing Mothers**

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

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

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

362 **8.4 Pediatric Use**

363 The safety and effectiveness of ZIAGEN have been established in pediatric patients
364 3 months to 13 years of age. Use of ZIAGEN in these age-groups is supported by
365 pharmacokinetic trials and evidence from adequate and well-controlled trials of ZIAGEN in
366 adults and pediatric patients [see *Dosage and Administration (2.2)*, *Clinical Pharmacology*
367 *(12.3)*, *Clinical Studies (14.2)*].

368 **8.5 Geriatric Use**

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

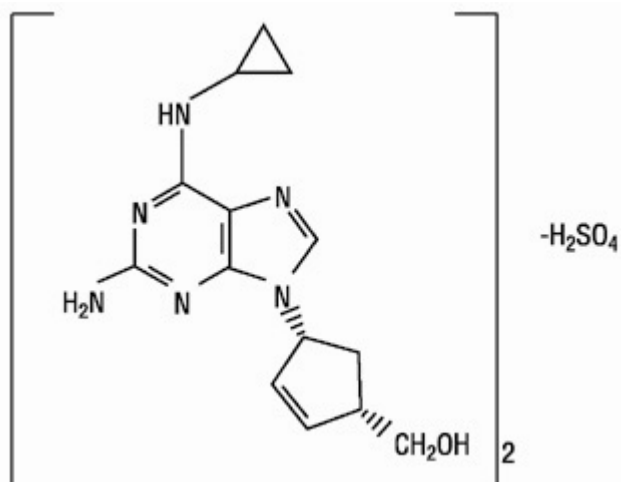
373 **10 OVERDOSAGE**

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

376 **11 DESCRIPTION**

377 ZIAGEN is the brand name for abacavir sulfate, a synthetic carbocyclic nucleoside
378 analogue with inhibitory activity against HIV-1. The chemical name of abacavir sulfate is
379 (1*S*,*cis*)-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate
380 (salt) (2:1). Abacavir sulfate is the enantiomer with 1*S*, 4*R* absolute configuration on the
381 cyclopentene ring. It has a molecular formula of $(C_{14}H_{18}N_6O)_2 \cdot H_2SO_4$ and a molecular weight
382 of 670.76 daltons. It has the following structural formula:

383



384

385

386 Abacavir sulfate is a white to off-white solid with a solubility of approximately
387 77 mg/mL in distilled water at 25°C. It has an octanol/water (pH 7.1 to 7.3) partition coefficient
388 (log *P*) of approximately 1.20 at 25°C.

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

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

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

401 **12 CLINICAL PHARMACOLOGY**

402 **12.1 Mechanism of Action**

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

404 **12.3 Pharmacokinetics**

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

409 *Absorption and Bioavailability:* Abacavir was rapidly and extensively absorbed after
410 oral administration. The geometric mean absolute bioavailability of the tablet was 83%. After
411 oral administration of 300 mg twice daily in 20 subjects, the steady-state peak serum abacavir
412 concentration (C_{max}) was 3.0 ± 0.89 mcg/mL (mean \pm SD) and $AUC_{(0-12\text{ hr})}$ was
413 6.02 ± 1.73 mcg•hr/mL. After oral administration of a single dose of 600 mg of abacavir in
414 20 subjects, C_{max} was 4.26 ± 1.19 mcg/mL (mean \pm SD) and AUC_{∞} was
415 11.95 ± 2.51 mcg•hr/mL.

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

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

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

425 dehydrogenase (to form the 5'-carboxylic acid) and glucuronyl transferase (to form the
426 5'-glucuronide). The metabolites do not have antiviral activity. In vitro experiments reveal that
427 abacavir does not inhibit human CYP3A4, CYP2D6, or CYP2C9 activity at clinically relevant
428 concentrations.

429 **Elimination:** Elimination of abacavir was quantified in a mass balance trial following
430 administration of a 600-mg dose of ¹⁴C-abacavir: 99% of the radioactivity was recovered, 1.2%
431 was excreted in the urine as abacavir, 30% as the 5'-carboxylic acid metabolite, 36% as the
432 5'-glucuronide metabolite, and 15% as unidentified minor metabolites in the urine. Fecal
433 elimination accounted for 16% of the dose.

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

436 **Effects of Food on Oral Absorption:** Bioavailability of abacavir tablets was assessed in
437 the fasting and fed states. There was no significant difference in systemic exposure (AUC_{∞}) in
438 the fed and fasting states; therefore, ZIAGEN Tablets may be administered with or without food.
439 Systemic exposure to abacavir was comparable after administration of ZIAGEN Oral Solution
440 and ZIAGEN Tablets. Therefore, these products may be used interchangeably.

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

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

453 **Pediatric Patients:** The pharmacokinetics of abacavir have been studied after either
454 single or repeat doses of ZIAGEN in 68 pediatric subjects. Following multiple-dose
455 administration of ZIAGEN 8 mg/kg twice daily, steady-state $AUC_{(0-12 \text{ hr})}$ and C_{\max} were
456 9.8 ± 4.56 mcg•hr/mL and 3.71 ± 1.36 mcg/mL (mean \pm SD), respectively [see *Use in Specific*
457 *Populations (8.4)*]. In addition, to support dosing of ZIAGEN scored tablet (300 mg) for
458 pediatric patients 14 kg to greater than 30 kg, analysis of actual and simulated pharmacokinetic
459 data indicated comparable exposures are expected following administration of 300 mg scored
460 tablet and the 8 mg/kg dosing regimen using oral solution.

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

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

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

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

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

479 *Ethanol:* Due to the common metabolic pathways of abacavir and ethanol via alcohol
480 dehydrogenase, the pharmacokinetic interaction between abacavir and ethanol was studied in
481 24 HIV-1-infected male subjects. Each subject received the following treatments on separate
482 occasions: a single 600-mg dose of abacavir, 0.7 g/kg ethanol (equivalent to 5 alcoholic drinks),
483 and abacavir 600 mg plus 0.7 g/kg ethanol. Coadministration of ethanol and abacavir resulted in
484 a 41% increase in abacavir AUC_∞ and a 26% increase in abacavir t_{1/2}. In males, abacavir had no
485 effect on the pharmacokinetic properties of ethanol, so no clinically significant interaction is
486 expected in men. This interaction has not been studied in females.

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

494 **12.4 Microbiology**

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

503 **Antiviral Activity:** The antiviral activity of abacavir against HIV-1 was evaluated against
504 a T-cell tropic laboratory strain HIV-1_{III B} in lymphoblastic cell lines, a monocyte/macrophage
505 tropic laboratory strain HIV-1_{BaL} in primary monocytes/macrophages, and clinical isolates in
506 peripheral blood mononuclear cells. The concentration of drug necessary to effect viral
507 replication by 50 percent (EC₅₀) ranged from 3.7 to 5.8 μM (1 μM = 0.28 mcg/mL) and 0.07 to
508 1.0 μM against HIV-1_{III B} and HIV-1_{BaL}, respectively, and was 0.26 ± 0.18 μM against 8 clinical
509 isolates. The EC₅₀ values of abacavir against different HIV-1 clades (A-G) ranged from 0.0015
510 to 1.05 μM, and against HIV-2 isolates, from 0.024 to 0.49 μM. Abacavir had synergistic
511 activity in cell culture in combination with the nucleoside reverse transcriptase inhibitor (NRTI)
512 zidovudine, the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, and the
513 protease inhibitor (PI) amprenavir; and additive activity in combination with the NRTIs
514 didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine. Ribavirin (50 μM)
515 had no effect on the anti-HIV-1 activity of abacavir in cell culture.

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

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

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

542 **13 NONCLINICAL TOXICOLOGY**

543 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

552 Mutagenicity: Abacavir induced chromosomal aberrations both in the presence and
553 absence of metabolic activation in an in vitro cytogenetic study in human lymphocytes. Abacavir
554 was mutagenic in the absence of metabolic activation, although it was not mutagenic in the
555 presence of metabolic activation in an L5178Y mouse lymphoma assay. Abacavir was
556 clastogenic in males and not clastogenic in females in an in vivo mouse bone marrow
557 micronucleus assay.

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

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

563 **13.2 Animal Toxicology and/or Pharmacology**

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

567 **14 CLINICAL STUDIES**

568 **14.1 Adults**

569 Therapy-Naive Adults: CNA30024 was a multicenter, double-blind, controlled trial in
570 which 649 HIV-1-infected, therapy-naive adults were randomized and received either ZIAGEN
571 (300 mg twice daily), lamivudine (150 mg twice daily), and efavirenz (600 mg once daily); or
572 zidovudine (300 mg twice daily), lamivudine (150 mg twice daily), and efavirenz (600 mg once
573 daily). The duration of double-blind treatment was at least 48 weeks. Trial participants were
574 male (81%), Caucasian (51%), black (21%), and Hispanic (26%). The median age was 35 years;
575 the median pretreatment CD4+ cell count was 264 cells/mm³, and median plasma HIV-1 RNA
576 was 4.79 log₁₀ copies/mL. The outcomes of randomized treatment are provided in Table 7.
577

578 **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%

579 ^a Subjects achieved and maintained confirmed HIV-1 RNA ≤ 50 copies/mL (< 400 copies/mL)
580 through Week 48 (Roche AMPLICOR Ultrasensitive HIV-1 MONITOR[®] standard test 1.0
581 PCR).

582 ^b Includes viral rebound, insufficient viral response according to the investigator, and failure to
583 achieve confirmed ≤ 50 copies/mL by Week 48.

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

586

587 After 48 weeks of therapy, the median CD4+ cell count increases from baseline were
588 209 cells/mm³ in the group receiving ZIAGEN and 155 cells/mm³ in the zidovudine group.
589 Through Week 48, 8 subjects (2%) in the group receiving ZIAGEN (5 CDC classification C
590 events and 3 deaths) and 5 subjects (2%) on the zidovudine arm (3 CDC classification C
591 events and 2 deaths) experienced clinical disease progression.

592 CNA3005 was a multicenter, double-blind, controlled trial in which 562 HIV-1-infected,
593 therapy-naive adults were randomized to receive either ZIAGEN (300 mg twice daily) plus
594 COMBIVIR[®] (lamivudine 150 mg/zidovudine 300 mg twice daily), or indinavir (800 mg 3 times
595 a day) plus COMBIVIR twice daily. The trial was stratified at randomization by pre-entry
596 plasma HIV-1 RNA 10,000 to 100,000 copies/mL and plasma HIV-1 RNA greater than
597 100,000 copies/mL. Trial participants were male (87%), Caucasian (73%), black (15%), and
598 Hispanic (9%). At baseline the median age was 36 years; the median baseline CD4+ cell count
599 was 360 cells/mm³, and median baseline plasma HIV-1 RNA was 4.8 log₁₀ copies/mL.
600 Proportions of subjects with plasma HIV-1 RNA less than 400 copies/mL (using Roche
601 AMPLICOR HIV-1 MONITOR Test) through 48 weeks of treatment are summarized in Table 8.
602

603 **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%

604 ^a Subjects achieved and maintained confirmed HIV-1 RNA <400 copies/mL.

605 ^b Includes viral rebound and failure to achieve confirmed <400 copies/mL by Week 48.

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

608

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

610

611 **Table 9. Proportions of Responders Through Week 48 By Screening Plasma HIV-1 RNA**
612 **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

613

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

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

622 CNA30021 was an international, multicenter, double-blind, controlled trial in which
623 770 HIV-1-infected, therapy-naive adults were randomized and received either abacavir 600 mg
624 once daily or abacavir 300 mg twice daily, both in combination with lamivudine 300 mg once
625 daily and efavirenz 600 mg once daily. The double-blind treatment duration was at least
626 48 weeks. Trial participants had a mean age of 37 years; were male (81%), Caucasian (54%),
627 black (27%), and American Hispanic (15%). The median baseline CD4+ cell count was
628 262 cells/mm³ (range 21 to 918 cells/mm³) and the median baseline plasma HIV-1 RNA was
629 4.89 log₁₀ copies/mL (range: 2.60 to 6.99 log₁₀ copies/mL).

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

631

632 **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%

633 ^a Subjects achieved and maintained confirmed HIV-1 RNA <50 copies/mL (<400 copies/mL)
634 through Week 48 (Roche AMPLICOR Ultrasensitive HIV-1 MONITOR standard test version
635 1.0).

636 ^b Includes viral rebound, failure to achieve confirmed <50 copies/mL (<400 copies/mL) by
637 Week 48, and insufficient viral load response.

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

640

641 After 48 weeks of therapy, the median CD4+ cell count increases from baseline were
642 188 cells/mm³ in the group receiving abacavir 600 mg once daily and 200 cells/mm³ in the group
643 receiving abacavir 300 mg twice daily. Through Week 48, 6 subjects (2%) in the group receiving
644 ZIAGEN 600 mg once daily (4 CDC classification C events and 2 deaths) and 10 subjects (3%)
645 in the group receiving ZIAGEN 300 mg twice daily (7 CDC classification C events and 3 deaths)
646 experienced clinical disease progression. None of the deaths were attributed to trial medications.

647 **14.2 Pediatric Trials**

648 Therapy-Experienced Pediatric Subjects: CNA3006 was a randomized, double-blind
649 trial comparing ZIAGEN 8 mg/kg twice daily plus lamivudine 4 mg/kg twice daily plus
650 zidovudine 180 mg/m² twice daily versus lamivudine 4 mg/kg twice daily plus zidovudine
651 180 mg/m² twice daily. Two hundred and five therapy-experienced pediatric subjects were
652 enrolled: female (56%), Caucasian (17%), black (50%), Hispanic (30%), median age of
653 5.4 years, baseline CD4+ cell percent greater than 15% (median = 27%), and median baseline
654 plasma HIV-1 RNA of 4.6 log₁₀ copies/mL. Eighty percent and 55% of subjects had prior
655 therapy with zidovudine and lamivudine, respectively, most often in combination. The median
656 duration of prior nucleoside analogue therapy was 2 years. At 16 weeks the proportion of
657 subjects responding based on plasma HIV-1 RNA less than or equal to 400 copies/mL was
658 significantly higher in subjects receiving ZIAGEN plus lamivudine plus zidovudine compared
659 with subjects receiving lamivudine plus zidovudine, 13% versus 2%, respectively. Median
660 plasma HIV-1 RNA changes from baseline were -0.53 log₁₀ copies/mL in the group receiving
661 ZIAGEN plus lamivudine plus zidovudine compared with -0.21 log₁₀ copies/mL in the group
662 receiving lamivudine plus zidovudine. Median CD4+ cell count increases from baseline were

663 69 cells/mm³ in the group receiving ZIAGEN plus lamivudine plus zidovudine and 9 cells/mm³
664 in the group receiving lamivudine plus zidovudine.

665 **15 REFERENCES**

666 1. Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study Group. *Lancet*.
667 2008;371 (9622):1417-1426.

668 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

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

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

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

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

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

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

683 **17 PATIENT COUNSELING INFORMATION**

684 See FDA-approved patient labeling (Medication Guide)

685 **17.1 Information About Therapy With ZIAGEN**

686 Hypersensitivity Reaction: Inform patients:

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

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

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

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

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

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

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

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

736

737 COMBIVIR, EPIVIR, EPZICOM, TRIZIVIR, and ZIAGEN are registered trademarks of ViiV
738 Healthcare.

739

740

741 Manufactured for:



742 ViiV Healthcare
743 Research Triangle Park, NC 27709

744

745

746 by:



747 GlaxoSmithKline
748 Research Triangle Park, NC 27709

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752 ZGN:PI

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755 **MEDICATION GUIDE**

756

757 **ZIAGEN® (ZY-uh-jen)**

758

(abacavir sulfate)

759

Tablets and Oral Solution

760

761

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

766

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

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

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

777

	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

778

779

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

780

Carry this Warning Card with you at all times.

781

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

790

791

792

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

793

794

795

796

797

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

798

799

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

800

- you feel very weak or tired

801

- you have unusual (not normal) muscle pain

802

- you have trouble breathing

803

- you have stomach pain with nausea and vomiting

804

- you feel cold, especially in your arms and legs

805

- you feel dizzy or light-headed

806

- you have a fast or irregular heartbeat

807 **3. Serious liver problems. Some people who have taken medicines like**
808 **ZIAGEN have developed serious liver problems called hepatotoxicity,**
809 **with liver enlargement (hepatomegaly) and fat in the liver (steatosis).**
810 **Hepatomegaly with steatosis is a serious medical emergency that can**
811 **cause death.**

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

- 814 • your skin or the white part of your eyes turns yellow (jaundice)
- 815 • your urine turns dark
- 816 • your bowel movements (stools) turn light in color
- 817 • you don't feel like eating food for several days or longer
- 818 • you feel sick to your stomach (nausea)
- 819 • you have lower stomach area (abdominal) pain

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

823

824 **What is ZIAGEN?**

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

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

834

835 **Who should not take ZIAGEN?**

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

- 837 • **are allergic to abacavir or any of the ingredients in ZIAGEN. See the**
838 **end of this Medication Guide for a complete list of ingredients in**
839 **ZIAGEN.**
- 840 • **have certain liver problems.**

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

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

- 843 • **have been tested and know whether or not you have a particular gene**
844 **variation called HLA-B*5701.**

- 845 • **have hepatitis B virus infection or have other liver problems.**
- 846 • **have heart problems, smoke, or have diseases that increase your risk**
- 847 **of heart disease such as high blood pressure, high cholesterol, or**
- 848 **diabetes.**
- 849 • **are pregnant or plan to become pregnant.** It is not known if ZIAGEN will
- 850 harm your unborn baby. Talk to your healthcare provider if you are pregnant or
- 851 plan to become pregnant.
- 852 **Pregnancy Registry.** If you take ZIAGEN while you are pregnant, talk to your
- 853 healthcare provider about how you can take part in the Pregnancy Registry for
- 854 ZIAGEN. The purpose of the pregnancy registry is to collect information about
- 855 the health of you and your baby.
- 856 • **are breastfeeding or plan to breastfeed. Do not breastfeed.** We do not
- 857 know if ZIAGEN can be passed to your baby in your breast milk and whether it
- 858 could harm your baby. Also, mothers with HIV-1 should not breastfeed because
- 859 HIV-1 can be passed to the baby in the breast milk.

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

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

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

- 863 • alcohol
- 864 • methadone
- 865 • TRIZIVIR (abacavir sulfate, lamivudine, and zidovudine)
- 866 • EPZICOM (abacavir sulfate and lamivudine)

867 Ask your healthcare provider if you are not sure if you take one of the medicines

868 listed above.

869 ZIAGEN may affect the way other medicines work, and other medicines may affect

870 how ZIAGEN works.

871 Know the medicines you take. Keep a list of your medicines with you to show to

872 your healthcare provider and pharmacist when you get a new medicine.

873

874 **How should I take ZIAGEN?**

- 875 • **Take ZIAGEN exactly as your healthcare provider tells you to take it.**
- 876 • **ZIAGEN is taken by mouth as a tablet or a strawberry- and banana-**
- 877 **flavored liquid.**
- 878 • ZIAGEN may be taken with or without food.
- 879 • Do not skip doses.
- 880 • Children aged 3 months and older can also take ZIAGEN. The child's healthcare
- 881 provider will decide the right dose and whether the child should take the tablet

882 or liquid, based on the child's weight. The dose should not be more than the
883 recommended adult dose.

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

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

889

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

891 • **ZIAGEN can cause serious side effects including allergic reactions, lactic**
892 **acidosis, and liver problems. See "What is the most important**
893 **information I should know about ZIAGEN?"**

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

898 • **Changes in body fat (fat redistribution).** Changes in body fat (lipoatrophy or
899 lipodystrophy) can happen in some people taking antiretroviral medicines
900 including ZIAGEN.

901 These changes may include:

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

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

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

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

908 • bad dreams or sleep problems

909 • nausea

910 • headache

911 • tiredness

912 • vomiting

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

914 • fever and chills

915 • nausea

916 • vomiting

917 • rash

918 • ear, nose, or throat infections

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

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

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

925

926 **How should I store ZIAGEN?**

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

928 • Do not freeze ZIAGEN.

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

930

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

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

933 • **Do not share needles or other injection equipment.**

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

936 • **Do not have any kind of sex without protection.** Always practice safe sex
937 by using a latex or polyurethane condom to lower the chance of sexual contact
938 with semen, vaginal secretions, or blood.

939

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

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

949

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

951

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

953 **Tablets**

954 Active ingredient: abacavir sulfate

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

958 **Oral Solution**

959 Active ingredient: abacavir sulfate

960 Inactive ingredients: artificial strawberry and banana flavors, citric acid
961 (anhydrous), methylparaben and propylparaben (added as preservatives),
962 propylene glycol, saccharin sodium, sodium citrate (dihydrate), sorbitol solution,
963 and water.

964

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

966

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970 Manufactured for:



971

972 ViiV Healthcare

973 Research Triangle Park, NC 27709

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975 by:



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977 GlaxoSmithKline

978 Research Triangle Park, NC 27709

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