

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

TRIZIVIR (abacavir sulfate, lamivudine, and zidovudine) Tablets
Initial U.S. Approval: 2000

WARNING: RISK OF HYPERSENSITIVITY REACTIONS, HEMATOLOGIC TOXICITY, MYOPATHY, LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY, EXACERBATIONS OF HEPATITIS B

See full prescribing information for complete boxed warning.

- Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir-containing products. (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 TRIZIVIR as soon as a hypersensitivity reaction is suspected. Regardless of HLA-B*5701 status, permanently discontinue TRIZIVIR if hypersensitivity cannot be ruled out. (5.1)
- Following a hypersensitivity reaction to abacavir, NEVER restart TRIZIVIR or any other abacavir-containing product. (5.1)
- Hematologic toxicity, including neutropenia and anemia, has been associated with the use of zidovudine, a component of TRIZIVIR. (5.2)
- Symptomatic myopathy associated with prolonged use of zidovudine. (5.3)
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues. (5.4)
- Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine, a component of TRIZIVIR. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.5)

-----INDICATIONS AND USAGE-----

TRIZIVIR, a combination of abacavir, lamivudine, and zidovudine, each nucleoside analogue HIV-1 reverse transcriptase inhibitors, 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 and Adolescents: 1 tablet twice daily. (2.1)
- Not recommended in adolescents who weigh less than 40 kg. (2.1)
- Do not prescribe for patients requiring dosage adjustment or patients with hepatic impairment. (2.2)

-----DOSAGE FORMS AND STRENGTHS-----

Tablets contain 300 mg abacavir, 150 mg of lamivudine, and 300 mg of zidovudine. (3)

-----CONTRAINDICATIONS-----

- Previously demonstrated hypersensitivity to abacavir or any other component of the product. (4, 5.1, 6)
- Hepatic impairment. (4)

-----WARNINGS AND PRECAUTIONS-----

- See boxed warning for information about the following: hypersensitivity reactions, hematologic toxicity, myopathy, lactic acidosis and severe hepatomegaly, and severe acute exacerbations of hepatitis B. (5.1, 5.2, 5.3, 5.4, 5.5)
- Hepatic decompensation, some fatal, has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy and interferon alfa with or without ribavirin. Discontinue TRIZIVIR as medically appropriate and consider dose reduction or discontinuation of interferon alfa, ribavirin, or both. (5.6)
- Exacerbation of anemia has been reported in HIV-1/HCV co-infected patients receiving ribavirin and zidovudine. Coadministration of ribavirin and zidovudine is not advised. (5.6)
- Immune reconstitution syndrome (5.7) and redistribution/accumulation of body fat (5.8) have been reported in patients treated with combination antiretroviral therapy.
- TRIZIVIR should not be administered with other products containing abacavir, lamivudine, or zidovudine; or with emtricitabine. (5.11)

-----ADVERSE REACTIONS-----

The most commonly reported adverse reactions (incidence $\geq 10\%$) in clinical studies were nausea, headache, malaise and fatigue, and nausea and vomiting. (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-----

- Concomitant use with the following drugs should be avoided: stavudine (7.1), doxorubicin (7.2).
- Ethanol: Decreases the elimination of abacavir. (7.3)
- Bone marrow suppressive/cytotoxic agents: May increase the hematologic toxicity of zidovudine. (7.4)
- Methadone: An increased methadone dose may be required in a small number of patients. (7.6)

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

Pregnancy registry available. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE.

Revised: March 2011

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4 **EXACERBATIONS OF HEPATITIS B**

5 **Hypersensitivity Reactions:** Serious and sometimes fatal hypersensitivity reactions have
6 been associated with abacavir sulfate, a component of TRIZIVIR. Hypersensitivity to
7 abacavir is a multi-organ clinical syndrome usually characterized by a sign or symptom in
8 2 or more of the following groups: (1) fever, (2) rash, (3) gastrointestinal (including nausea,
9 vomiting, diarrhea, or abdominal pain), (4) constitutional (including generalized malaise,
10 fatigue, or achiness), and (5) respiratory (including dyspnea, cough, or pharyngitis).

11 **Discontinue TRIZIVIR as soon as a 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 TRIZIVIR if**
21 **hypersensitivity cannot be ruled out, even when other diagnoses are possible.**

22 **Following a hypersensitivity reaction to abacavir, NEVER restart TRIZIVIR 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 TRIZIVIR 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 **Hematologic Toxicity:** Zidovudine, a component of TRIZIVIR, has been associated with
30 hematologic toxicity, including neutropenia and severe anemia, particularly in patients
31 with advanced Human Immunodeficiency Virus (HIV-1) disease [see Warnings and
32 *Precautions (5.2)*].

33 **Myopathy:** Prolonged use of zidovudine has been associated with symptomatic myopathy
34 [see Warnings and Precautions (5.3)].

35 **Lactic Acidosis and Severe Hepatomegaly:** Lactic acidosis and severe hepatomegaly
36 with steatosis, including fatal cases, have been reported with the use of nucleoside

37 analogues alone or in combination, including abacavir, lamivudine, zidovudine, and other
38 antiretrovirals [see *Warnings and Precautions (5.4)*].

39 **Exacerbations of Hepatitis B:** Severe acute exacerbations of hepatitis B have been
40 reported in patients who are co-infected with hepatitis B virus (HBV) and HIV-1 and have
41 discontinued lamivudine, which is one component of TRIZIVIR. Hepatic function should
42 be monitored closely with both clinical and laboratory follow-up for at least several months
43 in patients who discontinue TRIZIVIR and are co-infected with HIV-1 and HBV. If
44 appropriate, initiation of anti-hepatitis B therapy may be warranted [see *Warnings and*
45 *Precautions (5.5)*].

46 **1 INDICATIONS AND USAGE**

47 TRIZIVIR is indicated in combination with other antiretrovirals or alone for the treatment
48 of HIV-1 infection.

49 Additional important information on the use of TRIZIVIR for treatment of HIV-1
50 infection:

- 51 • TRIZIVIR is one of multiple products containing abacavir. Before starting TRIZIVIR,
52 review medical history for prior exposure to any abacavir-containing product in order to
53 avoid reintroduction in a patient with a history of hypersensitivity to abacavir [see *Warnings*
54 *and Precautions (5.1)*, *Adverse Reactions (6)*].
- 55 • TRIZIVIR is a fixed-dose combination of 3 nucleoside analogues: abacavir, lamivudine, and
56 zidovudine and is intended only for patients whose regimen would otherwise include these
57 3 components.
- 58 • Limited data exist on the use of TRIZIVIR alone in patients with higher baseline viral load
59 levels (>100,000 copies/mL) [see *Clinical Studies (14)*].

60 **2 DOSAGE AND ADMINISTRATION**

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

67 **2.1 Adults and Adolescent Patients**

68 The recommended oral dose of TRIZIVIR is one tablet twice daily.

69 TRIZIVIR is not recommended in adolescents who weigh less than 40 kg because it is a
70 fixed-dose tablet and cannot be dose adjusted.

71 **2.2 Dosage Adjustment**

72 Because it is a fixed-dose combination, TRIZIVIR should not be prescribed for:

- 73 • patients requiring dosage adjustment such as those with creatinine clearance <50 mL/min,
- 74 • patients with hepatic impairment.

75 **3 DOSAGE FORMS AND STRENGTHS**

76 TRIZIVIR Tablets contain 300 mg of abacavir as abacavir sulfate, 150 mg of lamivudine,
77 and 300 mg of zidovudine. The tablets are blue-green, capsule-shaped, film-coated, and
78 imprinted with “GX LL1” on one side with no markings on the reverse side.

79 **4 CONTRAINDICATIONS**

80 TRIZIVIR Tablets are contraindicated in patients with:

- 81 • previously demonstrated hypersensitivity to abacavir or any other component of the product.
82 NEVER restart TRIZIVIR or any other abacavir-containing product following a
83 hypersensitivity reaction to abacavir, regardless of HLA-B*5701 status [*see Warnings and*
84 *Precautions (5.1), Adverse Reactions (6)*].
- 85 • hepatic impairment [*see Use in Specific Populations (8.7)*].

86 **5 WARNINGS AND PRECAUTIONS**

87 **5.1 Hypersensitivity Reaction**

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

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

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

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

106 Group 1: Fever

107 Group 2: Rash

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

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

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

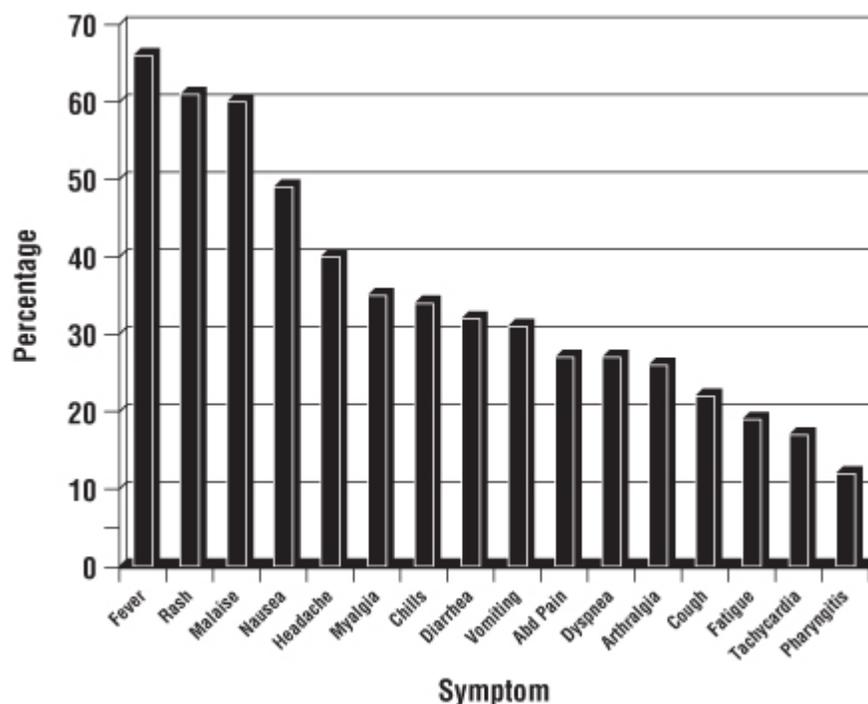
111 Hypersensitivity to abacavir following the presentation of a single sign or symptom has
112 been reported infrequently.

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

121 A study with ZIAGEN[®] (abacavir sulfate) used double-blind ascertainment of suspected
 122 hypersensitivity reactions. During the blinded portion of the study, suspected hypersensitivity to
 123 abacavir was reported by investigators in 9% of 324 subjects in the abacavir group and 3% of
 124 325 subjects in the zidovudine group.

125
 126
 127
 128

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



129 Other less common signs and symptoms of hypersensitivity include lethargy, myolysis,
 130 edema, abnormal chest x-ray findings (predominantly infiltrates, which can be localized), and
 131 paresthesia. Anaphylaxis, liver failure, renal failure, hypotension, adult respiratory distress
 132 syndrome, respiratory failure, and death have occurred in association with hypersensitivity
 133 reactions.

134
 135 Physical findings associated with hypersensitivity to abacavir in some subjects include
 136 lymphadenopathy, mucous membrane lesions (conjunctivitis and mouth ulcerations), and rash.
 137 The rash usually appears maculopapular or urticarial, but may be variable in appearance. There

138 have been reports of erythema multiforme. Hypersensitivity reactions have occurred without
139 rash.

140 Laboratory abnormalities associated with hypersensitivity to abacavir in some subjects
141 include elevated liver function tests, elevated creatinine phosphokinase, elevated creatinine, and
142 lymphopenia.

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

148 Following a hypersensitivity reaction to abacavir, NEVER restart TRIZIVIR or any other
149 abacavir-containing product because more severe symptoms can occur within hours and may
150 include life-threatening hypotension and death.

151 When therapy with TRIZIVIR has been discontinued for reasons other than symptoms of
152 a hypersensitivity reaction, and if reinitiation of abacavir is under consideration, carefully
153 evaluate the reason for discontinuation to ensure that the patient did not have symptoms of a
154 hypersensitivity reaction. If the patient is of unknown HLA-B*5701 status, screening for the
155 allele is recommended prior to reinitiation of TRIZIVIR.

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

160 If symptoms consistent with hypersensitivity are not identified, reintroduction can be
161 undertaken with continued monitoring for symptoms of a hypersensitivity reaction. Make
162 patients aware that a hypersensitivity reaction can occur with reintroduction of abacavir and that
163 abacavir reintroduction needs to be undertaken only if medical care can be readily accessed by
164 the patient or others.

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

167 CNA106030 (PREDICT-1), a randomized, double-blind study, evaluated the clinical
168 utility of prospective HLA-B*5701 screening on the incidence of abacavir hypersensitivity
169 reaction in abacavir-naive HIV-1-infected adults (n = 1,650). In this study, use of pre-therapy
170 screening for the HLA-B*5701 allele and exclusion of subjects with this allele reduced the
171 incidence of clinically suspected abacavir hypersensitivity reactions from 7.8% (66/847) to 3.4%
172 (27/803). Based on this study, it is estimated that 61% of patients with the HLA-B*5701 allele
173 will develop a clinically suspected hypersensitivity reaction during the course of abacavir
174 treatment compared with 4% of patients who do not have the HLA-B*5701 allele.

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

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

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

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

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

191 **5.2 Hemotologic Toxicity/Bone Marrow Suppression**

192 Zidovudine, a component of TRIZIVIR, has been associated with hematologic toxicity
193 including neutropenia and anemia, particularly in patients with advanced HIV-1 disease.
194 TRIZIVIR should be used with caution in patients who have bone marrow compromise
195 evidenced by granulocyte count less than 1,000 cells/mm³ or hemoglobin less than 9.5 g/dL.

196 Frequent blood counts are strongly recommended in patients with advanced HIV-1
197 disease who are treated with TRIZIVIR. Periodic blood counts are recommended for other
198 HIV-1-infected patients. If anemia or neutropenia develops, dosage interruption may be needed.

199 **5.3 Myopathy**

200 Myopathy and myositis, with pathological changes similar to that produced by HIV-1
201 disease, have been associated with prolonged use of zidovudine, and therefore may occur with
202 therapy with TRIZIVIR.

203 **5.4 Lactic Acidosis/Hepatomegaly With Steatosis**

204 Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been
205 reported with the use of nucleoside analogues alone or in combination, including abacavir,
206 lamivudine, zidovudine, and other antiretrovirals. A majority of these cases have been in women.
207 Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be
208 exercised when administering TRIZIVIR to any patient with known risk factors for liver disease;
209 however, cases have also been reported in patients with no known risk factors. Treatment with
210 TRIZIVIR should be suspended in any patient who develops clinical or laboratory findings
211 suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and
212 steatosis even in the absence of marked transaminase elevations).

213 **5.5 Patients With HIV-1 and Hepatitis B Virus Co-infection**

214 Posttreatment Exacerbations of Hepatitis: In clinical studies in non-HIV-1-infected
215 subjects treated with lamivudine for chronic HBV, clinical and laboratory evidence of
216 exacerbations of hepatitis have occurred after discontinuation of lamivudine. These
217 exacerbations have been detected primarily by serum ALT elevations in addition to

218 re-emergence of hepatitis B viral DNA (HBV DNA). Although most events appear to have been
219 self-limited, fatalities have been reported in some cases. Similar events have been reported from
220 post-marketing experience after changes from lamivudine-containing HIV-1 treatment regimens
221 to non-lamivudine-containing regimens in patients infected with both HIV-1 and HBV. The
222 causal relationship to discontinuation of lamivudine treatment is unknown. Patients should be
223 closely monitored with both clinical and laboratory follow-up for at least several months after
224 stopping treatment. There is insufficient evidence to determine whether reinitiation of
225 lamivudine alters the course of posttreatment exacerbations of hepatitis.

226 **Emergence of Lamivudine-Resistant HBV:** Safety and efficacy of lamivudine have
227 not been established for treatment of chronic hepatitis B in subjects dually infected with HIV-1
228 and HBV. In non-HIV-infected subjects treated with lamivudine for chronic hepatitis B,
229 emergence of lamivudine-resistant HBV has been detected and has been associated with
230 diminished treatment response (see full prescribing information for EPIVIR-HBV[®] [lamivudine]
231 for additional information). Emergence of hepatitis B virus variants associated with resistance to
232 lamivudine has also been reported in HIV-1-infected subjects who have received
233 lamivudine-containing antiretroviral regimens in the presence of concurrent infection with
234 hepatitis B virus.

235 **5.6 Use With Interferon- and Ribavirin-Based Regimens**

236 In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine
237 nucleoside analogues such as lamivudine and zidovudine. Although no evidence of a
238 pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic
239 suppression) was seen when ribavirin was coadministered with lamivudine or zidovudine in
240 HIV-1/HCV co-infected subjects [*see Clinical Pharmacology (12.3)*], hepatic decompensation
241 (some fatal) has occurred in HIV-1/HCV co-infected subjects receiving combination
242 antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin. Patients receiving
243 interferon alfa with or without ribavirin and TRIZIVIR should be closely monitored for
244 treatment-associated toxicities, especially hepatic decompensation, neutropenia, and anemia.
245 Discontinuation of TRIZIVIR should be considered as medically appropriate. Dose reduction or
246 discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening
247 clinical toxicities are observed, including hepatic decompensation (e.g., Child-Pugh greater than
248 6) (see the complete prescribing information for interferon and ribavirin).

249 Exacerbation of anemia has been reported in HIV-1/HCV co-infected patients receiving
250 ribavirin and zidovudine. Coadministration of ribavirin and TRIZIVIR is not advised.

251 **5.7 Immune Reconstitution Syndrome**

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

258 **5.8 Fat Redistribution**

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

264 **5.9 Myocardial Infarction**

265 In a published prospective, observational, epidemiological study designed to investigate
266 the rate of myocardial infarction in patients on combination antiretroviral therapy, the use of
267 abacavir within the previous 6 months was correlated with an increased risk of myocardial
268 infarction (MI).¹ In a sponsor-conducted pooled analysis of clinical studies, no excess risk of
269 myocardial infarction was observed in abacavir-treated subjects as compared with control
270 subjects. In totality, the available data from the observational cohort and from clinical studies are
271 inconclusive.

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

275 **5.10 Therapy-Experienced Patients**

276 In clinical studies, patients with prolonged prior nucleoside reverse transcriptase inhibitor
277 (NRTI) exposure or who had HIV-1 isolates that contained multiple mutations conferring
278 resistance to NRTIs had limited response to abacavir. The potential for cross-resistance between
279 abacavir and other NRTIs should be considered when choosing new therapeutic regimens in
280 therapy-experienced patients [*see Clinical Pharmacology (12.4)*].

281 **5.11 Use With Other Abacavir-, Lamivudine-, Zidovudine-, and/or Emtricitabine-**
282 **Containing Products**

283 TRIZIVIR is a fixed-dose combination of abacavir, lamivudine, and zidovudine and is
284 intended only for patients whose regimen would otherwise include these 3 components.
285 TRIZIVIR should not be administered concomitantly with other abacavir-, lamivudine-, or
286 zidovudine-containing products including ZIAGEN (abacavir) Tablets and Oral Solution,
287 EPIVIR[®] (lamivudine) Tablets and Oral Solution, EPIVIR-HBV (lamivudine) Tablets and Oral
288 Solution, RETROVIR[®] (zidovudine) Tablets, Capsules, Syrup, and IV Infusion, COMBIVIR[®]
289 (lamivudine and zidovudine) Tablets, EPZICOM[®] (abacavir sulfate and lamivudine) Tablets; or
290 emtricitabine-containing products, including ATRIPLA[®] (efavirenz, emtricitabine, and tenofovir
291 disoproxil fumarate) Tablets, EMTRIVA[®] (emtricitabine) Capsules and Oral Solution, or
292 TRUVADA[®] (emtricitabine and tenofovir) Tablets.

293 The complete prescribing information for all agents being considered for use with
294 TRIZIVIR should be consulted before combination therapy with TRIZIVIR is initiated.

295 **6 ADVERSE REACTIONS**

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

- 298 • Serious and sometimes fatal hypersensitivity reactions [*see Boxed Warning, Warnings and*
299 *Precautions (5.1)*].
- 300 • Hematologic toxicity, including neutropenia and anemia [*see Boxed Warning, Warnings and*
301 *Precautions (5.2)*].
- 302 • Symptomatic myopathy [*see Boxed Warning, Warnings and Precautions (5.3)*].
- 303 • Lactic acidosis and severe hepatomegaly with steatosis [*see Boxed Warning, Warnings and*
304 *Precautions (5.4)*].
- 305 • Acute exacerbations of hepatitis B [*see Boxed Warning, Warnings and Precautions (5.5)*].
- 306 • Hepatic decompensation in patients co-infected with HIV-1 and hepatitis C [*Warnings and*
307 *Precautions (5.6)*].
- 308 • Exacerbation of anemia in HIV-1/HCV co-infected patients receiving ribavirin and
309 zidovudine [*see Warnings and Precautions (5.6)*].
- 310 • Immune reconstitution syndrome [*see Warnings and Precautions (5.7)*].
- 311 • Fat redistribution [*see Warnings and Precautions (5.8)*].
- 312 • Myocardial infarction [*see Warnings and Precautions (5.9)*].

313 **6.1 Clinical Trials Experience**

314 Because clinical studies are conducted under widely varying conditions, adverse reaction
315 rates observed in the clinical studies of a drug cannot be directly compared with rates in the
316 clinical studies of another drug and may not reflect the rates observed in clinical practice.

317 Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or
318 severe) with a frequency greater than or equal to 5% during therapy with abacavir 300 mg twice
319 daily, lamivudine 150 mg twice daily, and zidovudine 300 mg twice daily compared with
320 indinavir 800 mg 3 times daily, lamivudine 150 mg twice daily, and zidovudine 300 mg twice
321 daily from CNA3005 are listed in Table 1.

322

323 **Table 1. Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate**
 324 **Intensity (Grades 2-4, ≥5% Frequency) in Therapy-Naive Adults (CNA3005) Through**
 325 **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%

326
 327 Five subjects receiving abacavir in study CNA3005 experienced worsening of
 328 pre-existing depression compared to none in the indinavir arm. The background rates of
 329 pre-existing depression were similar in the 2 treatment arms.

330 Laboratory Abnormalities: Laboratory abnormalities in study CNA3005 are listed in
 331 Table 2.

332

333 **Table 2. Treatment-Emergent Laboratory Abnormalities (Grades 3/4) in Study 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%)

334 ULN = Upper limit of normal.

335 n = Number of subjects assessed.

336

337 **Other Adverse Events:** In addition to adverse reactions in Tables 1 and 2, other adverse
338 events observed in the expanded access program for abacavir were pancreatitis and increased
339 GGT.

340 **6.2 Postmarketing Experience**

341 In addition to adverse reactions reported from clinical studies, the following reactions
342 have been identified during postmarketing use of abacavir, lamivudine, and/or zidovudine.
343 Because they are reported voluntarily from a population of unknown size, estimates of frequency
344 cannot be made. These reactions have been chosen for inclusion due to a combination of their
345 seriousness, frequency of reporting, or potential causal connection to abacavir, lamivudine and/or
346 zidovudine.

347 **Abacavir:**

348 **Cardiovascular:** Myocardial infarction.

349 **Skin:** Suspected Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis
350 (TEN) have been reported in patients receiving abacavir primarily in combination with
351 medications known to be associated with SJS and TEN, respectively. Because of the overlap of
352 clinical signs and symptoms between hypersensitivity to abacavir and SJS and TEN, and the
353 possibility of multiple drug sensitivities in some patients, abacavir should be discontinued and
354 not restarted in such cases.

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

356 **Abacavir, Lamivudine, and/or Zidovudine:**

357 **Body as a Whole:** Redistribution/accumulation of body fat [*see Warnings and*
358 *Precautions (5.8)*].

359 **Cardiovascular:** Cardiomyopathy.

360 **Digestive:** Stomatitis.

361 **Endocrine and Metabolic:** Gynecomastia, hyperglycemia.

362 *Gastrointestinal:* Anorexia and/or decreased appetite, abdominal pain, dyspepsia, oral
363 mucosal pigmentation.

364 *General:* Vasculitis, weakness.

365 *Hemic and Lymphatic:* Aplastic anemia, anemia (including pure red cell aplasia and
366 severe anemias progressing on therapy), lymphadenopathy, splenomegaly, thrombocytopenia.

367 *Hepatic:* Lactic acidosis and hepatic steatosis [*see Warnings and Precautions (5.4)*],
368 elevated bilirubin, elevated transaminases, posttreatment exacerbation of hepatitis B [*see*
369 *Warnings and Precautions (5.5)*].

370 *Hypersensitivity:* Sensitization reactions (including anaphylaxis), urticaria.

371 *Musculoskeletal:* Arthralgia, myalgia, muscle weakness, CPK elevation,
372 rhabdomyolysis.

373 *Nervous:* Dizziness, paresthesia, peripheral neuropathy, seizures.

374 *Psychiatric:* Insomnia and other sleep disorders.

375 *Respiratory:* Abnormal breath sounds/wheezing.

376 *Skin:* Alopecia, erythema multiforme, Stevens-Johnson syndrome.

377 **7 DRUG INTERACTIONS**

- 378 • No drug interaction studies have been conducted using TRIZIVIR Tablets [*see Clinical*
379 *Pharmacology (12.3)*].

380 **7.1 Antiretroviral Agents**

381 Zidovudine: *Stavudine:* Concomitant use of zidovudine with stavudine should be
382 avoided since an antagonistic relationship has been demonstrated in vitro.

383 *Nucleoside Analogues Affecting DNA Replication:* Some nucleoside analogues
384 affecting DNA replication, such as ribavirin, antagonize the in vitro antiviral activity of
385 zidovudine against HIV-1; concomitant use of such drugs should be avoided.

386 **7.2 Doxorubicin**

387 Zidovudine: Concomitant use of zidovudine with doxorubicin should be avoided since
388 an antagonistic relationship has been demonstrated in vitro.

389 **7.3 Ethanol**

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

393 **7.4 Hematologic/Bone Marrow Suppressive/Cytotoxic Agents**

394 Zidovudine: Coadministration of ganciclovir, interferon alfa, ribavirin, and other bone
395 marrow suppressive or cytotoxic agents may increase the hematologic toxicity of zidovudine.

396 **7.5 Interferon- and Ribavirin-Based Regimens**

397 Lamivudine: Although no evidence of a pharmacokinetic or pharmacodynamic
398 interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was
399 coadministered with lamivudine in HIV-1/HCV co-infected subjects, hepatic decompensation
400 (some fatal) has occurred in HIV-1/HCV co-infected subjects receiving combination

401 antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin [see Warnings and
402 Precautions (5.6), Clinical Pharmacology (12.3)].

403 **7.6 Methadone**

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

410 **7.7 Trimethoprim/Sulfamethoxazole (TMP/SMX)**

411 Lamivudine: No change in dose of either drug is recommended [see Clinical
412 Pharmacology (12.3)]. There is no information regarding the effect on lamivudine
413 pharmacokinetics of higher doses of TMP/SMX such as those used to treat PCP.

414 **8 USE IN SPECIFIC POPULATIONS**

415 **8.1 Pregnancy**

416 TRIZIVIR: Pregnancy Category C. There are no adequate and well-controlled studies of
417 TRIZIVIR in pregnant women. Reproduction studies with abacavir, lamivudine, and zidovudine
418 have been performed in animals (see Abacavir, Lamivudine, and Zidovudine sections below).
419 TRIZIVIR should be used during pregnancy only if the potential benefits outweigh the risks.

420 Abacavir: Studies in pregnant rats showed that abacavir is transferred to the fetus
421 through the placenta. Fetal malformations (increased incidences of fetal anasarca and skeletal
422 malformations) and developmental toxicity (depressed fetal body weight and reduced
423 crown-rump length) were observed in rats at a dose which produced 35 times the human
424 exposure, based on AUC. Embryonic and fetal toxicities (increased resorptions, decreased fetal
425 body weights) and toxicities to the offspring (increased incidence of stillbirth and lower body
426 weights) occurred at half of the above-mentioned dose in separate fertility studies conducted in
427 rats. In the rabbit, no developmental toxicity and no increases in fetal malformations occurred at
428 doses that produced 8.5 times the human exposure at the recommended dose based on AUC.

429 Lamivudine: Studies in pregnant rats showed that lamivudine is transferred to the fetus
430 through the placenta. Reproduction studies with orally administered lamivudine have been
431 performed in rats and rabbits at doses producing plasma levels up to approximately 35 times that
432 for the recommended adult HIV dose. No evidence of teratogenicity due to lamivudine was
433 observed. Evidence of early embryoletality was seen in the rabbit at exposure levels similar to
434 those observed in humans, but there was no indication of this effect in the rat at exposure levels
435 up to 35 times those in humans.

436 Zidovudine: Reproduction studies with orally administered zidovudine in the rat and in
437 the rabbit at doses up to 500 mg/kg/day revealed no evidence of teratogenicity with zidovudine.
438 Zidovudine treatment resulted in embryo/fetal toxicity as evidenced by an increase in the
439 incidence of fetal resorptions in rats given 150 or 450 mg/kg/day and rabbits given

440 500 mg/kg/day. The doses used in the teratology studies resulted in peak zidovudine plasma
441 concentrations (after one half of the daily dose) in rats 66 to 226 times, and in rabbits 12 to
442 87 times, mean steady-state peak human plasma concentrations (after one sixth of the daily dose)
443 achieved with the recommended daily dose (100 mg every 4 hours). In an additional teratology
444 study in rats, a dose of 3,000 mg/kg/day (very near the oral median lethal dose in rats of
445 approximately 3,700 mg/kg) caused marked maternal toxicity and an increase in the incidence of
446 fetal malformations. This dose resulted in peak zidovudine plasma concentrations 350 times peak
447 human plasma concentrations. No evidence of teratogenicity was seen in this experiment at doses
448 of 600 mg/kg/day or less. Two rodent carcinogenicity studies were conducted [*see Nonclinical*
449 *Toxicology (13.1)*].

450 Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant
451 women exposed to TRIZIVIR or other antiretroviral agents, an Antiretroviral Pregnancy Registry
452 has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

453 **8.3 Nursing Mothers**

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

456 Abacavir, Lamivudine, and Zidovudine: Lamivudine and zidovudine are excreted in
457 human breast milk; abacavir and lamivudine are secreted into the milk of lactating rats.

458 Because of both the potential for HIV-1 transmission and the potential for serious adverse
459 reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving
460 TRIZIVIR.

461 **8.4 Pediatric Use**

462 TRIZIVIR is not intended for use in pediatric patients and is not recommended in
463 adolescents who weigh less than 40 kg because it is a fixed-dose tablet that cannot be adjusted
464 for these patient populations.

465 Therapy-Experienced Pediatric Patients: A randomized, double-blind study,
466 CNA3006, compared ZIAGEN plus lamivudine and zidovudine versus lamivudine and
467 zidovudine in pediatric subjects, most of whom were extensively pretreated with nucleoside
468 analogue antiretroviral agents. Subjects in this study had a limited response to abacavir.

469 **8.5 Geriatric Use**

470 Clinical studies of abacavir, lamivudine, and zidovudine did not include sufficient
471 numbers of subjects aged 65 and over to determine whether they respond differently from
472 younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting
473 the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease
474 or other drug therapy [*see Dosage and Administration (2.3), Use in Specific Populations (8.6)*].

475 **8.6 Patients With Impaired Renal Function**

476 TRIZIVIR is not recommended for patients with impaired renal function (i.e., creatinine
477 clearance <50 mL/min) because TRIZIVIR is a fixed-dose combination and the dosage of the
478 individual components cannot be adjusted.

479 **8.7 Patients With Impaired Hepatic Function**

480 TRIZIVIR is contraindicated for patients with hepatic impairment because TRIZIVIR is a
481 fixed-dose combination and the dosage of the individual components cannot be adjusted.

482 10 OVERDOSAGE

483 **Abacavir:** There is no known antidote for abacavir. It is not known whether abacavir can
484 be removed by peritoneal dialysis or hemodialysis.

485 **Lamivudine:** One case of an adult ingesting 6 grams of lamivudine was reported; there
486 were no clinical signs or symptoms noted and hematologic tests remained normal. It is not
487 known whether lamivudine can be removed by peritoneal dialysis or hemodialysis.

488 **Zidovudine:** Acute overdoses of zidovudine have been reported in pediatric patients and
489 adults. These involved exposures up to 50 grams. The only consistent findings were nausea and
490 vomiting. Other reported occurrences included headache, dizziness, drowsiness, lethargy, and
491 confusion. Hematologic changes were transient. All patients recovered. Hemodialysis and
492 peritoneal dialysis appear to have a negligible effect on the removal of zidovudine, while
493 elimination of its primary metabolite, 3'-azido-3'-deoxy-5'-O-β-D-glucopyranuronosylthymidine
494 (GZDV), is enhanced.

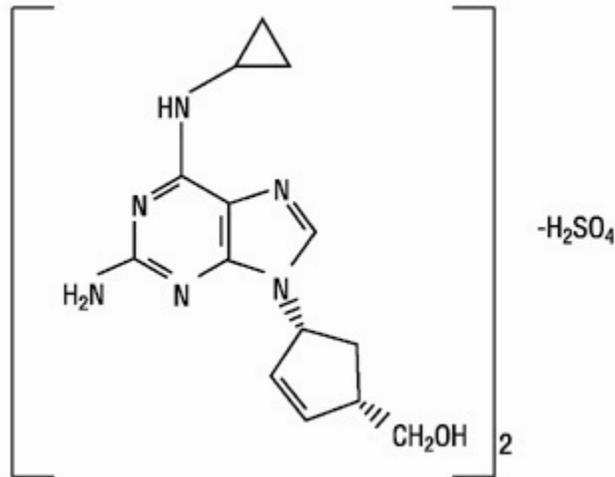
495 11 DESCRIPTION

496 **TRIZIVIR:** TRIZIVIR Tablets contain the following 3 synthetic nucleoside analogues:
497 abacavir sulfate (ZIAGEN), lamivudine (also known as EPIVIR or 3TC), and zidovudine (also
498 known as RETROVIR, azidothymidine, or ZDV) with inhibitory activity against HIV-1.

499 TRIZIVIR Tablets are for oral administration. Each film-coated tablet contains the active
500 ingredients 300 mg of abacavir as abacavir sulfate, 150 mg of lamivudine, and 300 mg of
501 zidovudine, and the inactive ingredients magnesium stearate, microcrystalline cellulose, and
502 sodium starch glycolate. The tablets are coated with a film (OPADRY® green 03B11434) that is
503 made of FD&C Blue No. 2, hypromellose, polyethylene glycol, titanium dioxide, and yellow
504 iron oxide.

505 **Abacavir Sulfate:** The chemical name of abacavir sulfate is (1*S*,*cis*)-4-[2-amino-6-
506 (cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1). Abacavir
507 sulfate is the enantiomer with *1S*, *4R* absolute configuration on the cyclopentene ring. It has a
508 molecular formula of (C₁₄H₁₈N₆O)₂•H₂SO₄ and a molecular weight of 670.76 daltons. It has the
509 following structural formula:

510



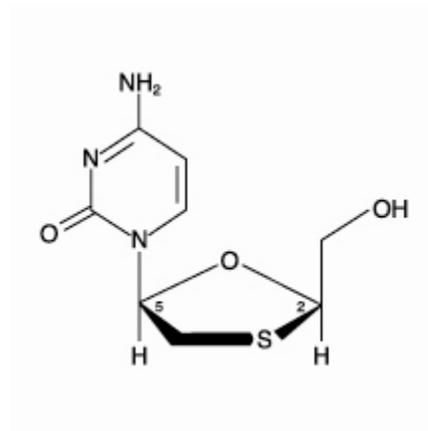
511
512

513 Abacavir sulfate is a white to off-white solid with a solubility of approximately
514 77 mg/mL in distilled water at 25°C.

515 In vivo, abacavir sulfate dissociates to its free base, abacavir. In this insert, all dosages
516 for ZIAGEN (abacavir sulfate) are expressed in terms of abacavir.

517 **Lamivudine:** The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-
518 hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)enantiomer of a
519 dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2',3'-dideoxy, 3'-
520 thiacytidine. It has a molecular formula of C₈H₁₁N₃O₃S and a molecular weight of 229.3 daltons.
521 It has the following structural formula:

522

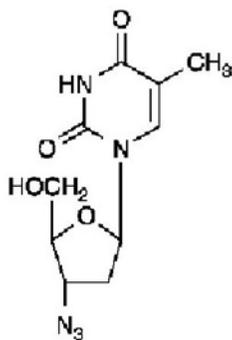


523
524

525 Lamivudine is a white to off-white crystalline solid with a solubility of approximately
526 70 mg/mL in water at 20°C.

527 **Zidovudine:** The chemical name of zidovudine is 3'-azido-3'-deoxythymidine. It has a
528 molecular formula of C₁₀H₁₃N₅O₄ and a molecular weight of 267.24 daltons. It has the following
529 structural formula:

530



531
532
533
534

Zidovudine is a white to beige, crystalline solid with a solubility of 20.1 mg/mL in water at 25°C.

535 12 CLINICAL PHARMACOLOGY

536 12.1 Mechanism of Action

537 TRIZIVIR is an antiviral agent [see *Clinical Pharmacology* (12.4)].

538 12.3 Pharmacokinetics

539 Pharmacokinetics in Adults: *TRIZIVIR*: In a single-dose, 3-way crossover
540 bioavailability study of 1 *TRIZIVIR* Tablet versus 1 *ZIAGEN* Tablet (300 mg), 1 *EPIVIR* Tablet
541 (150 mg), plus 1 *RETROVIR* Tablet (300 mg) administered simultaneously in healthy subjects
542 (n = 24), there was no difference in the extent of absorption, as measured by the area under the
543 plasma concentration-time curve (AUC) and maximal peak concentration (C_{max}), of all
544 3 components. One *TRIZIVIR* Tablet was bioequivalent to 1 *ZIAGEN* Tablet (300 mg),
545 1 *EPIVIR* Tablet (150 mg), plus 1 *RETROVIR* Tablet (300 mg) following single-dose
546 administration to fasting healthy subjects (n = 24).

547 *Abacavir*: Following oral administration, abacavir is rapidly absorbed and extensively
548 distributed. Binding of abacavir to human plasma proteins is approximately 50%. Binding of
549 abacavir to plasma proteins was independent of concentration. Total blood and plasma
550 drug-related radioactivity concentrations are identical, demonstrating that abacavir readily
551 distributes into erythrocytes. The primary routes of elimination of abacavir are metabolism by
552 alcohol dehydrogenase to form the 5'-carboxylic acid and glucuronyl transferase to form the
553 5'-glucuronide.

554 *Lamivudine*: Following oral administration, lamivudine is rapidly absorbed and
555 extensively distributed. Binding to plasma protein is low. Approximately 70% of an intravenous
556 dose of lamivudine is recovered as unchanged drug in the urine. Metabolism of lamivudine is a
557 minor route of elimination. In humans, the only known metabolite is the trans-sulfoxide
558 metabolite (approximately 5% of an oral dose after 12 hours).

559 *Zidovudine*: Following oral administration, zidovudine is rapidly absorbed and
560 extensively distributed. Binding to plasma protein is low. Zidovudine is eliminated primarily by
561 hepatic metabolism. The major metabolite of zidovudine is GZDV. GZDV AUC is about 3-fold
562 greater than the zidovudine AUC. Urinary recovery of zidovudine and GZDV accounts for 14%

563 and 74% of the dose following oral administration, respectively. A second metabolite, 3'-amino-
564 3'-deoxythymidine (AMT), has been identified in plasma. The AMT AUC was one-fifth of the
565 zidovudine AUC.

566 In humans, abacavir, lamivudine, and zidovudine are not significantly metabolized by
567 cytochrome P450 enzymes.

568 The pharmacokinetic properties of abacavir, lamivudine, and zidovudine in fasting
569 subjects are summarized in Table 3.

570

571 **Table 3. Pharmacokinetic Parameters^a for Abacavir, Lamivudine, and Zidovudine in**
572 **Adults**

Parameter	Abacavir		Lamivudine		Zidovudine	
Oral bioavailability (%)	86 ± 25	n = 6	86 ± 16	n = 12	64 ± 10	n = 5
Apparent volume of distribution (L/kg)	0.86 ± 0.15	n = 6	1.3 ± 0.4	n = 20	1.6 ± 0.6	n = 8
Systemic clearance (L/hr/kg)	0.80 ± 0.24	n = 6	0.33 ± 0.06	n = 20	1.6 ± 0.6	n = 6
Renal clearance (L/hr/kg)	.007 ± .008	n = 6	0.22 ± 0.06	n = 20	0.34 ± 0.05	n = 9
Elimination half-life (hr)	1.45 ± 0.32	n = 20	5 to 7 ^b		0.5 to 3 ^b	

573 ^a Data presented as mean ± standard deviation except where noted.

574 ^b Approximate range.

575

576 **Effect of Food on Absorption of TRIZIVIR:** Administration with food in a single-dose
577 bioavailability study resulted in lower C_{max}, similar to results observed previously for the
578 reference formulations. The average [90% CI] decrease in abacavir, lamivudine, and zidovudine
579 C_{max} was 32% [24% to 38%], 18% [10% to 25%], and 28% [13% to 40%], respectively, when
580 administered with a high-fat meal, compared with administration under fasted conditions.
581 Administration of TRIZIVIR with food did not alter the extent of abacavir, lamivudine, and
582 zidovudine absorption (AUC), as compared with administration under fasted conditions (n = 24)
583 [see *Dosage and Administration* (2.1)].

584 **Special Populations: Renal Impairment: TRIZIVIR:** Because lamivudine and
585 zidovudine require dose adjustment in the presence of renal insufficiency, TRIZIVIR is not
586 recommended for use in patients with creatinine clearance <50 mL/min [see *Use in Specific*
587 *Populations* (8.6)].

588 **Hepatic Impairment: TRIZIVIR:** TRIZIVIR is contraindicated for patients with
589 impaired hepatic function because TRIZIVIR is a fixed-dose combination and the dosage of the
590 individual components cannot be adjusted. Abacavir is contraindicated in patients with moderate to
591 severe hepatic impairment and dose reduction is required in patients with mild hepatic impairment.

592 **Pregnancy:** See *Use in Specific Populations* (8.1).

593 **Abacavir and Lamivudine:** No data are available on the pharmacokinetics of
594 abacavir or lamivudine during pregnancy.

595 *Zidovudine:* Zidovudine pharmacokinetics have been studied in a Phase 1 study of
596 8 women during the last trimester of pregnancy. As pregnancy progressed, there was no evidence
597 of drug accumulation. The pharmacokinetics of zidovudine were similar to that of nonpregnant
598 adults. Consistent with passive transmission of the drug across the placenta, zidovudine
599 concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at
600 delivery. Although data are limited, methadone maintenance therapy in 5 pregnant women did
601 not appear to alter zidovudine pharmacokinetics. In a nonpregnant adult population, a potential
602 for interaction has been identified [*see Use in Specific Populations (8.1)*].

603 *Nursing Mothers:* See *Use in Specific Populations (8.3)*.

604 *Abacavir:* No data are available on the pharmacokinetics of abacavir in nursing
605 mothers.

606 *Lamivudine:* Samples of breast milk obtained from 20 mothers receiving
607 lamivudine monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice
608 daily and 300 mg zidovudine twice daily) had measurable concentrations of lamivudine.

609 *Zidovudine:* After administration of a single dose of 200 mg zidovudine to
610 13 HIV-infected women, the mean concentration of zidovudine was similar in human milk and
611 serum [*see Use in Specific Populations (8.3)*].

612 *Pediatric Patients:* TRIZIVIR is not intended for use in pediatric patients. TRIZIVIR
613 is not recommended in adolescents who weigh less than 40 kg because it is a fixed-dose tablet
614 that cannot be dose adjusted for this patient population.

615 *Geriatric Patients:* The pharmacokinetics of abacavir, lamivudine, and zidovudine
616 have not been studied in subjects over 65 years of age.

617 *Gender:*

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

621 *Lamivudine and Zidovudine:* A pharmacokinetic study in healthy male (n = 12)
622 and female (n = 12) subjects showed no gender differences in zidovudine exposure (AUC_{∞}) or
623 lamivudine (AUC_{∞}) normalized for body weight.

624 *Race:*

625 *Abacavir:* There are no significant differences between blacks and
626 Caucasians in abacavir pharmacokinetics.

627 *Lamivudine:* There are no significant racial differences in lamivudine
628 pharmacokinetics.

629 *Zidovudine:* The pharmacokinetics of zidovudine with respect to race have not
630 been determined.

631 Drug Interactions: The drug interactions described below are based on studies
632 conducted with the individual nucleoside analogues.

633 *Cytochrome P450:* In humans, abacavir, lamivudine, and zidovudine are not
634 significantly metabolized by cytochrome P450 enzymes; therefore, it is unlikely that clinically
635 significant drug interactions will occur with drugs metabolized through these pathways.

636 *Glucuronyl Transferase:* Due to the common metabolic pathways of abacavir and
637 zidovudine via glucuronyl transferase, 15 HIV-1-infected subjects were enrolled in a crossover
638 study evaluating single doses of abacavir (600 mg), lamivudine (150 mg), and zidovudine
639 (300 mg) alone or in combination. Analysis showed no clinically relevant changes in the
640 pharmacokinetics of abacavir with the addition of lamivudine or zidovudine or the combination
641 of lamivudine and zidovudine. Lamivudine exposure (AUC decreased 15%) and zidovudine
642 exposure (AUC increased 10%) did not show clinically relevant changes with concurrent
643 abacavir.

644 *Lamivudine and Zidovudine:* No clinically significant alterations in lamivudine or
645 zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-1-infected adult subjects
646 given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine
647 (300 mg q 12 hr).

648 *Methadone:* In a study of 11 HIV-1-infected subjects receiving
649 methadone-maintenance therapy (40 mg and 90 mg daily), with 600 mg of ZIAGEN twice daily
650 (twice the currently recommended dose), oral methadone clearance increased 22% (90% CI: 6%
651 to 42%) [see *Drug Interactions* (7.6)].

652 *Ribavirin:* In vitro data indicate ribavirin reduces phosphorylation of lamivudine,
653 stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or
654 intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss
655 of HIV-1/HCV virologic suppression) interaction was observed when ribavirin and lamivudine
656 (n = 18), stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug
657 regimen to HIV-1/HCV co-infected subjects [see *Warnings and Precautions* (5.6)].

658 The effects of other coadministered drugs on abacavir, lamivudine, or zidovudine are
659 provided in Table 4.

660

661 **Table 4. Effect of Coadministered Drugs on Abacavir, Lamivudine, and Zidovudine AUC^a**
Note: ROUTINE DOSE MODIFICATION OF ABACAVIR, LAMIVUDINE, AND ZIDOVUDINE IS NOT WARRANTED WITH COADMINISTRATION OF THE FOLLOWING DRUGS.

Drugs That May Alter Lamivudine Blood Concentrations					
Coadministered Drug and Dose	Lamivudine Dose	n	Lamivudine Concentrations		Concentration of Coadministered Drug
			AUC	Variability	
Nelfinavir 750 mg q 8 hr x 7 to 10 days	single 150 mg	11	↑10%	95% CI: 1% to 20%	↔
Trimethoprim 160 mg/ Sulfamethoxazole 800 mg daily x 5 days	single 300 mg	14	↑43%	90% CI: 32% to 55%	↔
Drugs That May Alter Zidovudine Blood Concentrations					
Coadministered Drug and Dose	Zidovudine Dose	n	Zidovudine Concentrations		Concentration of Coadministered Drug
			AUC	Variability	
Atovaquone 750 mg q 12 hr with food	200 mg q 8 hr	14	↑31%	Range: 23% to 78% ^b	↔
Clarithromycin 500 mg twice daily	100 mg q 4 hr x 7 days	4	↓AUC 12%	Range: ↓34% to ↑14%	Not Reported
Fluconazole 400 mg daily	200 mg q 8 hr	12	↑74%	95% CI: 54% to 98%	Not Reported
Methadone 30 to 90 mg daily	200 mg q 4 hr	9	↑43%	Range: 16% to 64% ^b	↔
Nelfinavir 750 mg q 8 hr x 7 to 10 days	single 200 mg	11	↓35%	Range: 28% to 41%	↔
Probenecid 500 mg q 6 hr x 2 days	2 mg/kg q 8 hr x 3 days	3	↑106%	Range: 100% to 170% ^b	Not Assessed
Rifampin 600 mg daily x 14 days	200 mg q 8 hr x 14 days	8	↓AUC 47%	90% CI: 41% to 53%	Not Assessed
Ritonavir 300 mg q 6 hr x 4	200 mg q 8 hr x 4 days	9	↓25%	95% CI: 15% to 34%	↔

days					
Valproic acid 250 mg or 500 mg q 8 hr x 4 days	100 mg q 8 hr x 4 days	6	↑80%	Range: 64% to 130% ^b	Not Assessed
Drugs That May Alter Abacavir Blood Concentrations					
Coadministered Drug and Dose	Abacavir Dose	n	Abacavir Concentrations		Concentration of Coadministered Drug
			AUC	Variability	
Ethanol 0.7 g/kg	single 600 mg	24	↑41%	90% CI: 35% to 48%	↔

662 ↑ = Increase; ↓ = Decrease; ↔ = no significant change; AUC = area under the concentration
663 versus time curve; CI = confidence interval.

664 ^a See *Drug Interactions (7)* for additional information on drug interactions.

665 ^b Estimated range of percent difference.

666

667 12.4 Microbiology

668 **Mechanism of Action: *Abacavir*:** Abacavir is a carbocyclic synthetic nucleoside
669 analogue. Abacavir is converted by cellular enzymes to the active metabolite, carbovir
670 triphosphate (CBV-TP), an analogue of deoxyguanosine-5'-triphosphate (dGTP). CBV-TP
671 inhibits the activity of HIV-1 reverse transcriptase (RT) both by competing with the natural
672 substrate dGTP and by its incorporation into viral DNA. The lack of a 3'-OH group in the
673 incorporated nucleotide analogue prevents the formation of the 5' to 3' phosphodiester linkage
674 essential for DNA chain elongation, and therefore, the viral DNA growth is terminated. CBV-TP
675 is a weak inhibitor of cellular DNA polymerases α , β , and γ .

676 ***Lamivudine*:** Lamivudine is a synthetic nucleoside analogue. Intracellularly,
677 lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate
678 (3TC-TP). The principal mode of action of 3TC-TP is inhibition of RT via DNA chain
679 termination after incorporation of the nucleotide analogue. 3TC-TP is a weak inhibitor of cellular
680 DNA polymerases α , β , and γ .

681 ***Zidovudine*:** Zidovudine is a synthetic nucleoside analogue. Intracellularly,
682 zidovudine is phosphorylated to its active 5'-triphosphate metabolite, zidovudine triphosphate
683 (ZDV-TP). The principal mode of action of ZDV-TP is inhibition of RT via DNA chain
684 termination after incorporation of the nucleotide analogue. ZDV-TP is a weak inhibitor of the
685 cellular DNA polymerases α and γ and has been reported to be incorporated into the DNA of
686 cells in culture.

687 **Antiviral Activity: *Abacavir*:** The antiviral activity of abacavir against HIV-1 was
688 evaluated against a T-cell tropic laboratory strain HIV-1_{IIB} in lymphoblastic cell lines, a
689 monocyte/macrophage tropic laboratory strain HIV-1_{BaL} in primary monocytes/macrophages,
690 and clinical isolates in peripheral blood mononuclear cells. The concentration of drug necessary
691 to effect viral replication by 50 percent (EC₅₀) ranged from 3.7 to 5.8 μ M (1 μ M = 0.28 mcg/mL)

692 and 0.07 to 1.0 μM against HIV-1_{IIIB} and HIV-1_{BaL}, respectively, and was $0.26 \pm 0.18 \mu\text{M}$
693 against 8 clinical isolates. The EC₅₀ values of abacavir against different HIV-1 clades (A-G)
694 ranged from 0.0015 to 1.05 μM , and against HIV-2 isolates, from 0.024 to 0.49 μM . Abacavir
695 had synergistic activity in cell culture in combination with the NRTI zidovudine, the
696 non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, and the protease inhibitor
697 (PI) amprenavir; and additive activity in combination with the NRTIs didanosine, emtricitabine,
698 lamivudine, stavudine, tenofovir, and zalcitabine. Ribavirin (50 μM) had no effect on the anti-
699 HIV-1 activity of abacavir in cell culture.

700 **Lamivudine:** The antiviral activity of lamivudine against HIV-1 was assessed in a
701 number of cell lines (including monocytes and fresh human peripheral blood lymphocytes) using
702 standard susceptibility assays. EC₅₀ values (50% effective concentrations) were in the range of
703 0.003 to 15 μM (1 μM = 0.23 mcg/mL). HIV-1 from therapy-naive subjects with no amino acid
704 substitutions associated with resistance gave median EC₅₀ values of 0.429 μM (range: 0.200 to
705 2.007 μM) from Virco (n = 92 baseline samples from COLA40263) and 2.35 μM (1.37 to
706 3.68 μM) from Monogram Biosciences (n = 135 baseline samples from ESS30009). The EC₅₀
707 values of lamivudine against different HIV-1 clades (A-G) ranged from 0.001 to 0.120 μM , and
708 against HIV-2 isolates from 0.003 to 0.120 μM in peripheral blood mononuclear cells. Ribavirin
709 (50 μM) decreased the anti-HIV-1 activity of lamivudine by 3.5-fold in MT-4 cells.

710 **Zidovudine:** The antiviral activity of zidovudine against HIV-1 was assessed in a
711 number of cell lines (including monocytes and fresh human peripheral blood lymphocytes). The
712 EC₅₀ and EC₉₀ values for zidovudine were 0.01 to 0.49 μM (1 μM = 0.27 mcg/mL) and 0.1 to
713 9 μM , respectively. HIV-1 from therapy-naive subjects with no amino acid substitutions
714 associated with resistance gave median EC₅₀ values of 0.011 μM (range: 0.005 to 0.110 μM)
715 from Virco (n = 92 baseline samples from COLA40263) and 0.0017 μM (0.006 to 0.0340 μM)
716 from Monogram Biosciences (n = 135 baseline samples from ESS30009). The EC₅₀ values of
717 zidovudine against different HIV-1 clades (A-G) ranged from 0.00018 to 0.02 μM , and against
718 HIV-2 isolates from 0.00049 to 0.004 μM . In cell culture drug combination studies, zidovudine
719 demonstrates synergistic activity with the NRTIs abacavir, didanosine, lamivudine, and
720 zalcitabine; the NNRTIs delavirdine and nevirapine; and the PIs indinavir, nelfinavir, ritonavir,
721 and saquinavir; and additive activity with interferon alfa. Ribavirin has been found to inhibit the
722 phosphorylation of zidovudine in cell culture.

723 **Resistance:** HIV-1 isolates with reduced sensitivity to abacavir, lamivudine, or
724 zidovudine have been selected in cell culture and were also obtained from subjects treated with
725 abacavir, lamivudine, and zidovudine, or the combination of lamivudine and zidovudine.

726 **Abacavir:** Genotypic analysis of isolates selected in cell culture and recovered from
727 abacavir-treated subjects demonstrated that amino acid substitutions K65R, L74V, Y115F, and
728 M184V/I in HIV-1 RT contributed to abacavir resistance. In a study of subjects receiving
729 abacavir once or twice daily in combination with lamivudine and efavirenz once daily, 39%
730 (7/18) of the isolates from subjects who experienced virologic failure in the abacavir once-daily
731 arm had a >2.5-fold decrease in abacavir susceptibility with a median-fold decrease of 1.3

732 (range: 0.5 to 11) compared with 29% (5/17) of the failure isolates in the twice-daily arm with a
733 median-fold decrease of 0.92 (range: 0.7 to 13).

734 *Lamivudine*: Genotypic analysis of isolates selected in cell culture and recovered
735 from lamivudine-treated subjects showed that the resistance was due to a specific amino acid
736 substitution in the HIV-1 RT at codon 184 changing the methionine to either valine or isoleucine
737 (M184V/I).

738 *Zidovudine*: Genotypic analyses of the isolates selected in cell culture and recovered
739 from zidovudine-treated subjects showed mutations in the HIV-1 RT gene resulting in 6 amino
740 acid substitutions (M41L, D67N, K70R, L210W, T215Y or F, and K219Q) that confer
741 zidovudine resistance. In general, higher levels of resistance were associated with greater number
742 of mutations. In some subjects harboring zidovudine-resistant virus at baseline, phenotypic
743 sensitivity to zidovudine was restored by 12 weeks of treatment with lamivudine and zidovudine.
744 Combination therapy with lamivudine plus zidovudine delayed the emergence of substitutions
745 conferring resistance to zidovudine.

746 Cross-Resistance: Cross-resistance has been observed among NRTIs.

747 *Abacavir*: Isolates containing abacavir resistance-associated amino acid substitutions,
748 namely, K65R, L74V, Y115F, and M184V, exhibited cross-resistance to didanosine,
749 emtricitabine, lamivudine, tenofovir, and zalcitabine in cell culture and in subjects. The K65R
750 substitution can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, stavudine,
751 tenofovir, and zalcitabine; the L74V substitution can confer resistance to abacavir, didanosine,
752 and zalcitabine; and the M184V substitution can confer resistance to abacavir, didanosine,
753 emtricitabine, lamivudine, and zalcitabine. An increasing number of thymidine analogue
754 mutations (TAMs: M41L, D67N, K70R, L210W, T215Y/F, K219E/R/H/Q/N) is associated with
755 a progressive reduction in abacavir susceptibility.

756 *Lamivudine*: Cross-resistance to abacavir, didanosine, tenofovir, and zalcitabine has
757 been observed in some subjects harboring lamivudine-resistant HIV-1 isolates. In some subjects
758 treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple drugs,
759 including lamivudine, have emerged (see under Zidovudine below). Cross-resistance between
760 lamivudine and zidovudine has not been reported.

761 *Zidovudine*: In a study of 167 HIV-infected subjects, isolates (n = 2) with multi-drug
762 resistance to didanosine, lamivudine, stavudine, zalcitabine, and zidovudine were recovered from
763 subjects treated for ≥ 1 year with zidovudine plus didanosine or zidovudine plus zalcitabine. The
764 pattern of resistance-associated amino acid substitutions with such combination therapies was
765 different (A62V, V75I, F77L, F116Y, Q151M) from the pattern with zidovudine monotherapy,
766 with the Q151M substitution being most commonly associated with multi-drug resistance. The
767 substitution at codon 151 in combination with substitutions at 62, 75, 77, and 116 results in a
768 virus with reduced susceptibility to didanosine, lamivudine, stavudine, zalcitabine, and
769 zidovudine. TAMs are selected by zidovudine and confer cross-resistance to abacavir,
770 didanosine, stavudine, tenofovir, and zalcitabine.

771 **13 NONCLINICAL TOXICOLOGY**

772 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

773 Carcinogenicity:

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

782 *Lamivudine:* Long-term carcinogenicity studies with lamivudine in mice and rats
783 showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times
784 (rats) those observed in humans at the recommended therapeutic dose for HIV-1 infection.

785 *Zidovudine:* Zidovudine was administered orally at 3 dosage levels to separate groups
786 of mice and rats (60 females and 60 males in each group). Initial single daily doses were 30, 60,
787 and 120 mg/kg/day in mice and 80, 220, and 600 mg/kg/day in rats. The doses in mice were
788 reduced to 20, 30, and 40 mg/kg/day after day 90 because of treatment-related anemia, whereas
789 in rats only the high dose was reduced to 450 mg/kg per day on day 91 and then to
790 300 mg/kg/day on day 279.

791 In mice, 7 late-appearing (after 19 months) vaginal neoplasms (5 nonmetastasizing
792 squamous cell carcinomas, 1 squamous cell papilloma, and 1 squamous polyp) occurred in
793 animals given the highest dose. One late-appearing squamous cell papilloma occurred in the
794 vagina of a middle-dose animal. No vaginal tumors were found at the lowest dose.

795 In rats, 2 late-appearing (after 20 months), nonmetastasizing vaginal squamous cell
796 carcinomas occurred in animals given the highest dose. No vaginal tumors occurred at the low or
797 middle dose in rats. No other drug-related tumors were observed in either sex of either species.

798 At doses that produced tumors in mice and rats, the estimated drug exposure (as
799 measured by AUC) was approximately 3 times (mouse) and 24 times (rat) the estimated human
800 exposure at the recommended therapeutic dose of 100 mg every 4 hours.

801 Two transplacental carcinogenicity studies were conducted in mice. One study
802 administered zidovudine at doses of 20 mg/kg/day or 40 mg/kg/day from gestation day 10
803 through parturition and lactation with dosing continuing in offspring for 24 months postnatally.
804 At these doses, exposures were approximately 3 times the estimated human exposure at the
805 recommended doses. After 24 months at the 40-mg/kg/day dose, an increase in incidence of
806 vaginal tumors was noted with no increase in tumors in the liver or lung or any other organ in
807 either gender. These findings are consistent with results of the standard oral carcinogenicity
808 study in mice, as described earlier. A second study administered zidovudine at maximum
809 tolerated doses of 12.5 mg/day or 25 mg/day (~1,000 mg/kg nonpregnant body weight or
810 ~450 mg/kg of term body weight) to pregnant mice from days 12 through 18 of gestation. There

811 was an increase in the number of tumors in the lung, liver, and female reproductive tracts in the
812 offspring of mice receiving the higher dose level of zidovudine.

813 It is not known how predictive the results of rodent carcinogenicity studies may be for
814 humans.

815 Mutagenicity:

816 *Abacavir:* Abacavir induced chromosomal aberrations both in the presence and
817 absence of metabolic activation in an in vitro cytogenetic study in human lymphocytes. Abacavir
818 was mutagenic in the absence of metabolic activation, although it was not mutagenic in the
819 presence of metabolic activation in an L5178Y/TK^{+/-} mouse lymphoma assay. Abacavir was
820 clastogenic in males and not clastogenic in females in an in vivo mouse bone marrow
821 micronucleus assay. Abacavir was not mutagenic in bacterial mutagenicity assays in the presence
822 and absence of metabolic activation.

823 *Lamivudine:* Lamivudine was mutagenic in an L5178Y/TK^{+/-} mouse lymphoma
824 assay and clastogenic in a cytogenetic assay using cultured human lymphocytes. Lamivudine
825 was negative in a microbial mutagenicity assay, in an in vitro cell transformation assay, in a rat
826 micronucleus test, in a rat bone marrow cytogenetic assay, and in an assay for unscheduled DNA
827 synthesis in rat liver.

828 *Zidovudine:* Zidovudine was mutagenic in an L5178Y/TK^{+/-} mouse lymphoma
829 assay, positive in an in vitro cell transformation assay, clastogenic in a cytogenetic assay using
830 cultured human lymphocytes, and positive in mouse and rat micronucleus tests after repeated
831 doses. It was negative in a cytogenetic study in rats given a single dose.

832 Impairment of Fertility:

833 *Abacavir:* Abacavir had no adverse effects on the mating performance or fertility of
834 male and female rats at a dose approximately 8 times the human exposure at the recommended
835 dose based on body surface area comparisons.

836 *Lamivudine:* In a study of reproductive performance, lamivudine, administered to
837 male and female rats at doses up to 130 times the usual adult dose based on body surface area
838 considerations, revealed no evidence of impaired fertility judged by conception rates and no
839 effect on the survival, growth, and development to weaning of the offspring.

840 *Zidovudine:* Zidovudine, administered to male and female rats at doses up to 7 times
841 the usual adult dose based on body surface area considerations, had no effect on fertility judged
842 by conception rates.

843 **13.2 Animal Toxicology and/or Pharmacology**

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

847 **14 CLINICAL STUDIES**

848 The following study was conducted with the individual components of TRIZIVIR [*see*
849 *Clinical Pharmacology (12.3)*].

850 **CNA3005** was a multicenter, double-blind, controlled study in which
 851 562 HIV-1-infected, therapy-naive adults were randomized to receive either ZIAGEN (300 mg
 852 twice daily) plus COMBIVIR (lamivudine 150 mg/zidovudine 300 mg twice daily), or indinavir
 853 (800 mg 3 times a day) plus COMBIVIR twice daily. The study was stratified at randomization
 854 by pre-entry plasma HIV-1 RNA 10,000 to 100,000 copies/mL and plasma HIV-1 RNA
 855 >100,000 copies/mL. Study participants were male (87%), Caucasian (73%), black (15%), and
 856 Hispanic (9%). At baseline the median age was 36 years, the median pretreatment CD4+ cell
 857 count was 360 cells/mm³, and median plasma HIV-1 RNA was 4.8 log₁₀ copies/mL. Proportions
 858 of subjects with plasma HIV-1 RNA <400 copies/mL (using Roche AMPLICOR HIV-1
 859 MONITOR[®] Test) through 48 weeks of treatment are summarized in Table 5.

860

861 **Table 5. 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%

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

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

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

866

867 Treatment response by plasma HIV-1 RNA strata is shown in Table 6.

868

869 **Table 6. Proportions of Responders Through Week 48 By Screening Plasma HIV-1 RNA**
 870 **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

871

872 In subjects with baseline viral load >100,000 copies/mL, percentages of subjects with
 873 HIV-1 RNA levels <50 copies/mL were 31% in the group receiving abacavir vs. 45% in the
 874 group receiving indinavir.

875 Through Week 48, an overall mean increase in CD4+ cell count of about 150 cells/mm³
 876 was observed in both treatment arms. Through Week 48, 9 subjects (3.4%) in the group receiving

877 abacavir sulfate (6 CDC classification C events and 3 deaths) and 3 subjects (1.5%) in the group
878 receiving indinavir (2 CDC classification C events and 1 death) experienced clinical disease
879 progression.

880 **15 REFERENCES**

881 1. Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study Group. *Lancet*.
882 2008;371 (9622):1417-1426.

883 **16 HOW SUPPLIED/STORAGE AND HANDLING**

884 TRIZIVIR is available as tablets. Each tablet contains 300 mg of abacavir as abacavir
885 sulfate, 150 mg of lamivudine, and 300 mg of zidovudine. The tablets are blue-green capsule-
886 shaped, film-coated, and imprinted with GX LL1 on one side with no markings on the reverse
887 side. They are packaged as follows:

888 Bottles of 60 Tablets (NDC 49702-217-18).

889 **Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) (see USP**
890 **Controlled Room Temperature).**

891 **17 PATIENT COUNSELING INFORMATION**

892 See Medication Guide.

893 Hypersensitivity Reaction: Inform patients:

- 894 • that a Medication Guide and Warning Card summarizing the symptoms of the abacavir
895 hypersensitivity reaction and other product information will be dispensed by the pharmacist
896 with each new prescription and refill of TRIZIVIR, and encourage the patient to read the
897 Medication Guide and Warning Card every time to obtain any new information that may be
898 present about TRIZIVIR. (The complete text of the Medication Guide is reprinted at the end
899 of this document.)
- 900 • to carry the Warning Card with them.
- 901 • how to identify a hypersensitivity reaction[see *Warnings and Precautions (5.1), Medication*
902 *Guide*].
- 903 • that if they develop symptoms consistent with a hypersensitivity reaction they should call
904 their doctor right away to determine if they should stop taking TRIZIVIR.
- 905 • that a hypersensitivity reaction can worsen and lead to hospitalization or death if TRIZIVIR
906 is not immediately discontinued.
- 907 • to not restart TRIZIVIR or any other abacavir-containing product following a
908 hypersensitivity reaction because more severe symptoms can occur within hours and may
909 include life-threatening hypotension and death.
- 910 • that a hypersensitivity reaction is usually reversible if it is detected promptly and TRIZIVIR
911 is stopped right away.
- 912 • that if they have interrupted TRIZIVIR for reasons other than symptoms of hypersensitivity
913 (for example, those who have an interruption in drug supply), a serious or fatal
914 hypersensitivity reaction may occur with reintroduction of abacavir.

- 915 • to not restart TRIZIVIR or any other abacavir-containing product without medical
916 consultation and that restarting abacavir needs to be undertaken only if medical care can be
917 readily accessed by the patient or others.
- 918 • TRIZIVIR should not be coadministered with ATRIPLA, COMBIVIR, EMTRIVA, EPIVIR,
919 EPIVIR-HBV, EPZICOM, RETROVIR (zidovudine), TRUVADA, or ZIAGEN.

920 Neutropenia and Anemia: Patients should be informed that the important toxicities
921 associated with zidovudine are neutropenia and/or anemia. They should be told of the extreme
922 importance of having their blood counts followed closely while on therapy, especially for
923 patients with advanced HIV-1 disease.

924 Lactic Acidosis/Hepatomegaly: Inform patients that some HIV medicines, including
925 TRIZIVIR, can cause a rare, but serious condition called lactic acidosis with liver enlargement
926 (hepatomegaly).

927 Co-infection With HIV-1 and HBV: Patients co-infected with HIV-1 and HBV should
928 be informed that deterioration of liver disease has occurred in some cases when treatment with
929 lamivudine was discontinued. Patients should be advised to discuss any changes in regimen with
930 their physician.

931 Redistribution/Accumulation of Body Fat: Inform patients that redistribution or
932 accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause
933 and long-term health effects of these conditions are not known at this time.

934 Information About HIV Infection: TRIZIVIR is not a cure for HIV infection and
935 patients may continue to experience illnesses associated with HIV infection, including
936 opportunistic infections. Patients should remain under the care of a physician when using
937 TRIZIVIR. Advise patients that the use of TRIZIVIR has not been shown to reduce the risk of
938 transmission of HIV to others through sexual contact or blood contamination. Patients should be
939 informed to take all HIV medications exactly as prescribed.

940
941 TRIZIVIR Tablets are for oral ingestion only.

942
943 COMBIVIR, EPIVIR, EPZICOM, RETROVIR, TRIZIVIR, and ZIAGEN are registered
944 trademarks of ViiV Healthcare.

945
946 Other brands are trademarks of their respective owners and are not trademarks of ViiV
947 Healthcare. The makers of these brands are not affiliated with and do not endorse ViiV
948 Healthcare or its products.

949
950 Manufactured for:



951
952 ViiV Healthcare

953 Research Triangle Park, NC 27709

954

955 by:



GlaxoSmithKline

956

957 GlaxoSmithKline

958 Research Triangle Park, NC 27709

959

960 Lamivudine is manufactured under agreement from

961 **Shire Pharmaceuticals Group plc**

962 Basingstoke, UK

963

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965

966 TRZ:xPI

967

968

MEDICATION GUIDE

TRIZIVIR® (TRY-zih-veer)

(abacavir sulfate, lamivudine, and zidovudine)

972

Tablets

973 Read this Medication Guide before you start taking TRIZIVIR and each time you get

974 a refill. There may be new information. This information does not take the place of

975 talking to your healthcare provider about your medical condition or your treatment.

976 Be sure to carry your TRIZIVIR Warning Card with you at all times.

977

978 **What is the most important information I should know about TRIZIVIR?**

979 **1. Serious allergic reaction (hypersensitivity reaction).** TRIZIVIR contains

980 abacavir (also contained in ZIAGEN® and EPZICOM®). Patients taking

981 TRIZIVIR may have a serious allergic reaction (hypersensitivity reaction) that

982 can cause death. Your risk of this allergic reaction is much higher if you have

983 a gene variation called HLA-B*5701. Your healthcare provider can determine

984 with a blood test if you have this gene variation.

985

986 **If you get a symptom from 2 or more of the following groups while**

987 **taking TRIZIVIR, call your healthcare provider right away to find out if**

988 **you should stop taking TRIZIVIR.**

	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

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

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

991 **If you stop TRIZIVIR because of an allergic reaction, never take**
 992 **TRIZIVIR (abacavir sulfate, lamivudine, and zidovudine) or any other**
 993 **abacavir-containing medicine (ZIAGEN and EPZICOM) again.** If you take
 994 TRIZIVIR or any other abacavir-containing medicine again after you have had
 995 an allergic reaction, **within hours** you may get **life-threatening symptoms**
 996 that may include **very low blood pressure** or **death**. If you stop TRIZIVIR,
 997 for any other reason, even for a few days, and you are not allergic to
 998 TRIZIVIR, talk with your healthcare provider before taking it again. Taking
 999 TRIZIVIR again can cause a serious allergic or life-threatening reaction, even if
 1000 you never had an allergic reaction to it before.

1001 **If your healthcare provider tells you that you can take TRIZIVIR again,**
 1002 **start taking it when you are around medical help or people who can**
 1003 **call a healthcare provider if you need one.**

2. **Blood problems.** RETROVIR[®], one of the medicines in TRIZIVIR, can cause serious blood cell problems. These include reduced numbers of white blood cells (neutropenia) and extremely reduced numbers of red blood cells (anemia). These blood cell problems are especially likely to happen in patients with advanced human immunodeficiency virus (HIV) disease or AIDS. Your doctor should be checking your blood cell counts regularly while you are taking TRIZIVIR. This is especially important if you have advanced HIV or AIDS. This is to make sure that any blood cell problems are found quickly.

3. **Lactic Acidosis (buildup of acid in the blood).** Some human immunodeficiency virus (HIV) medicines, including TRIZIVIR, 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.

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

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

4. Serious liver problems. Some people who have taken medicines like TRIZIVIR have developed serious liver problems called hepatotoxicity, with liver enlargement (hepatomegaly) and fat in the liver (steatosis). Hepatomegaly with steatosis is a serious medical emergency that can cause death.

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

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

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

1004 **5. Use with interferon and ribavirin-based regimens.** Worsening of liver
 1005 disease (sometimes resulting in death) has occurred in patients infected with
 1006 both HIV and hepatitis C virus who are taking anti-HIV medicines and are
 1007 also being treated for hepatitis C with interferon with or without ribavirin. If
 1008 you are taking TRIZIVIR as well as interferon with or without ribavirin and
 1009 you experience side effects, be sure to tell your healthcare provider.

1010 **6. If you have HIV and hepatitis B virus infection, your hepatitis B virus**
 1011 **infection may get worse if you stop taking TRIZIVIR.**

- Take TRIZIVIR exactly as prescribed.
- Do not run out of TRIZIVIR.
- Do not stop TRIZIVIR without talking to your healthcare provider.

Your healthcare provider should monitor your health and do regular blood tests to check your liver if you stop taking TRIZIVIR.

1012 **7. Muscle weakness (myopathy). RETROVIR, one of the medicines in**
 1013 **TRIZIVIR, can cause muscle weakness. This can be a serious**
 1014 **problem.**

1015 **What is TRIZIVIR?**

1016 TRIZIVIR is a prescription medicine used to treat HIV infection. TRIZIVIR contains
 1017 3 medicines: abacavir (ZIAGEN), lamivudine or 3TC (EPIVIR®), and zidovudine,

1018 AZT, or ZDV (RETROVIR). All 3 of these medicines are called nucleoside analogue
1019 reverse transcriptase inhibitors (NRTIs). When used together, they help lower the
1020 amount of HIV in your blood.

1021 • **TRIZIVIR does not cure HIV infection or AIDS.**

1022 • It is not known if TRIZIVIR will help you live longer or have fewer of the medical
1023 problems that people get with HIV or AIDS.

1024 • It is very important that you see your healthcare provider regularly while you are
1025 taking TRIZIVIR.

1026 **Who should not take TRIZIVIR?**

1027 **Do not take TRIZIVIR if you:**

1028 • **are allergic to abacavir or any of the ingredients in TRIZIVIR. See the**
1029 **end of this Medication Guide for a complete list of ingredients in**
1030 **TRIZIVIR.**

1031 • **have certain liver problems**

1032 • **are an adolescent who weighs less than 90 pounds.**

1033

What should I tell my healthcare provider before taking TRIZIVIR?

1034 **Before you take TRIZIVIR, tell your healthcare provider if you:**

1035 • **have been tested and know whether or not you have a particular gene**
1036 **variation called HLA-B*5701**

1037 • **have hepatitis B virus infection or have other liver problems**

1038 • **have kidney problems**

1039 • **have low blood cell counts (bone marrow problem).** Ask your doctor if you
1040 are not sure.

1041 • **have heart problems, smoke, or have diseases that increase your risk of**
1042 **heart disease such as high blood pressure, high cholesterol, or diabetes.**

1043 • **are pregnant or plan to become pregnant.** It is not known if TRIZIVIR will
1044 harm your unborn baby. Talk to your healthcare provider if you are pregnant or
1045 plan to become pregnant.

1046 **Pregnancy Registry.** If you take TRIZIVIR while you are pregnant, talk to your
1047 healthcare provider about how you can take part in the Pregnancy Registry for
1048 TRIZIVIR. The purpose of the pregnancy registry is to collect information about
1049 the health of you and your baby.

1050 • **are breastfeeding or plan to breastfeed.** TRIZIVIR can pass into your breast
1051 milk. You should not breastfeed if you are taking TRIZIVIR. If you are a woman
1052 who has or will have a baby while taking TRIZIVIR, talk to your healthcare
1053 provider about the best way to feed your baby. The Center for Disease Control
1054 and Prevention (CDC) recommends that HIV-infected mothers **not** breastfeed to
1055 avoid the risk of passing HIV infection to your baby.

1056 **Tell your healthcare provider about all the medicines you take**, including
1057 prescription and nonprescription medicines, vitamins, and herbal supplements.

1058 **Especially tell your healthcare provider if you take:**

- 1059 • alcohol
- 1060 • medicines used to treat hepatitis viruses such as interferon or ribavirin
- 1061 • methadone
- 1062 • BACTRIM[®], SEPTA[®] (trimethoprim [TMP/sulfamethoxazole SMX])
- 1063 • CYTOVENE[®], DHPG (ganciclovir)
- 1064 • interferon-alfa
- 1065 • ADRIAMYCIN[®] (doxorubicin)
- 1066 • COPEGUS[®], REBETOL[®], VIRAZOLE[®] (ribavirin)
- 1067 • any bone marrow suppressive medicines or cytotoxic medicines. Ask your doctor
1068 if you are not sure.
- 1069 • ATRIPLA[®] (efavirenz, emtricitabine, and tenofovir)
- 1070 • COMBIVIR[®] (lamivudine and zidovudine)
- 1071 • EMTRIVA[®] (emtricitabine)
- 1072 • EPIVIR or EPIVIR-HBV[®] (lamivudine, 3TC)
- 1073 • EPZICOM (abacavir sulfate and lamivudine)
- 1074 • RETROVIR (zidovudine)
- 1075 • TRUVADA[®] (emtricitabine and tenofovir)
- 1076 • ZERIT[®] (stavudine, d4T)
- 1077 • ZIAGEN (abacavir sulfate)

1078 Ask your healthcare provider if you are not sure if you take one of the medicines
1079 listed above.

1080 TRIZIVIR may affect the way other medicines work, and other medicines may affect
1081 how TRIZIVIR works.

1082 Know the medicines you take. Keep a list of your medicines with you to show to
1083 your healthcare provider and pharmacist when you get a new medicine.

1084 **How should I take TRIZIVIR?**

- 1085 • **Take TRIZIVIR exactly as your healthcare provider tells you to take it..**
- 1086 • TRIZIVIR may be taken with or without food.
- 1087 • Do not skip doses.
- 1088 • **Do not let your TRIZIVIR run out.**

1089 If you stop your anti-HIV medicines, even for a short time, the amount of virus in
1090 your blood may increase and the virus may become harder to treat. If you take
1091 too much TRIZIVIR, call your healthcare provider or poison control center or go
1092 to the nearest hospital emergency room right away.

1093 **What are the possible side effects of TRIZIVIR?**
1094 **TRIZIVIR can cause serious side effects including allergic reactions, lactic**
1095 **acidosis, and liver problems. See “What is the most important information**
1096 **I should know about TRIZIVIR?”**

- 1097 • **Blood problems.**
- 1098 • **Muscle weakness.**
- 1099 • **Changes in immune system (Immune Reconstitution Syndrome).** Your
1100 immune system may get stronger and begin to fight infections that have been
1101 hidden in your body for a long time. Tell your healthcare provider if you start
1102 having new or worse symptoms of infection after you start taking TRIZIVIR.
- 1103 • **Changes in body fat (fat redistribution).** Changes in body fat (lipoatrophy or
1104 lipodystrophy) can happen in some people taking antiretroviral medicines
1105 including TRIZIVIR.
1106 These changes may include:
 - 1107 ○ more fat in or around your trunk, upper back and neck (buffalo hump),
1108 breast or chest
 - 1109 ○ loss of fat in your legs, arms, or face
- 1110 • **Heart attack (myocardial infarction).** Some HIV medicines including
1111 TRIZIVIR may increase your risk of heart attack.

1112 **The most common side effects of TRIZIVIR include:**

- 1113 • nausea
- 1114 • headache
- 1115 • weakness or tiredness
- 1116 • vomiting
- 1117 • diarrhea
- 1118 • fever and/or chills
- 1119 • depression
- 1120 • muscle and joint pain
- 1121 • skin rashes
- 1122 • ear, nose, throat infections
- 1123 • cold symptoms
- 1124 • nervousness

1125 Tell your healthcare provider if you have any side effect that bothers you or that
1126 does not go away.

1127 These are not all the possible side effects of TRIZIVIR. For more information, ask
1128 your healthcare provider or pharmacist.

1129 Call your doctor for medical advice about side effects. You may report side effects
1130 to FDA at 1-800-FDA-1088.

1131 **How should I store TRIZIVIR?**

- 1132 • Store TRIZIVIR at 59°F to 86°F (15°C to 30°C).
1133 • **Keep TRIZIVIR and all medicines out of the reach of children.**

1134 **General information for safe and effective use of TRIZIVIR.**

1135 **TRIZIVIR does not stop you from spreading HIV to other people by sex,**
1136 **sharing needles, or being exposed to your blood.** Talk with your healthcare
1137 provider about safe sexual practices that protect your partner. Never share needles.
1138 Do not share personal items that can have blood or body fluids on them, like
1139 toothbrushes or razor blades.

1140

1141 Medicines are sometimes prescribed for purposes other than those listed in a
1142 Medication Guide. Do not use TRIZIVIR for a condition for which it was not
1143 prescribed. Do not give TRIZIVIR to other people, even if they have the same
1144 symptoms that you have. It may harm them.

1145 This Medication Guide summarizes the most important information about TRIZIVIR.
1146 If you would like more information, talk with your healthcare provider. You can ask
1147 your healthcare provider or pharmacist for the information about TRIZIVIR that is
1148 written for healthcare professionals.

1149 For more information go to www.TRIZIVIR.com or call 1-877-844-8872.

1150 **What are the ingredients in TRIZIVIR?**

1151 Active ingredients: abacavir sulfate, lamivudine, and zidovudine

1152 Inactive ingredients: magnesium stearate, microcrystalline cellulose, sodium starch
1153 glycolate, and OPADRY® green 03B11434, a film coating made of FD&C Blue No. 2,
1154 hypromellose, polyethylene glycol, titanium dioxide, and yellow iron oxide.

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1160 Manufactured for:



1161 ViiV Healthcare
1162 Research Triangle Park, NC 27709

1163

1164 by:



1165
1166 GlaxoSmithKline
1167 Research Triangle Park, NC 27709

1168 Lamivudine is manufactured under agreement from
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1170 Basingstoke, UK

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