

- 1 **ATRIPLA™**  
2 **(efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg)**  
3 **Tablets**  
4 **R<sub>x</sub> Only**

#### **WARNINGS**

**LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGS ALONE OR IN COMBINATION WITH OTHER ANTIRETROVIRALS (SEE WARNINGS).**

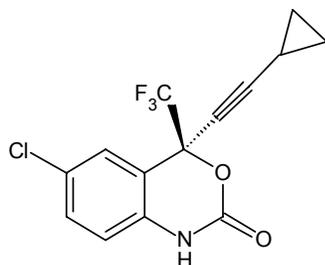
**ATRIPLA IS NOT APPROVED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION AND THE SAFETY AND EFFICACY OF ATRIPLA HAVE NOT BEEN ESTABLISHED IN PATIENTS COINFECTED WITH HBV AND HIV. SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO HAVE DISCONTINUED EMTRIVA OR VIREAD WHICH ARE COMPONENTS OF ATRIPLA. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO ARE COINFECTED WITH HIV AND HBV AND DISCONTINUE ATRIPLA. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS).**

#### **5 DESCRIPTION**

6 ATRIPLA™ is a fixed dose combination tablet containing efavirenz, emtricitabine, and  
7 tenofovir disoproxil fumarate (tenofovir DF). SUSTIVA is the brand name for efavirenz,  
8 a non-nucleoside reverse transcriptase inhibitor. EMTRIVA is the brand name for  
9 emtricitabine, a synthetic nucleoside analog of cytidine. VIREAD is the brand name for  
10 tenofovir DF, which is converted in vivo to tenofovir, an acyclic nucleoside phosphonate  
11 (nucleotide) analog of adenosine 5'-monophosphate. VIREAD and EMTRIVA are the  
12 components of TRUVADA.

13 ATRIPLA Tablets are for oral administration. Each tablet contains 600 mg of efavirenz,  
14 200 mg of emtricitabine, and 300 mg of tenofovir DF (which is equivalent to 245 mg of  
15 tenofovir disoproxil) as active ingredients. The tablets include the following inactive  
16 ingredients: croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate,  
17 microcrystalline cellulose, and sodium lauryl sulfate. The tablets are film-coated with a  
18 coating material containing black iron oxide, polyethylene glycol, polyvinyl alcohol, red  
19 iron oxide, talc, and titanium dioxide.

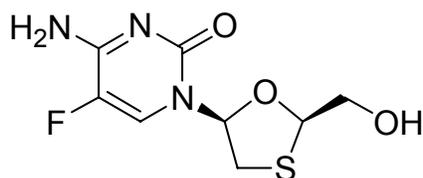
20 **Efavirenz:** Efavirenz is chemically described as (S)-6-chloro-4-(cyclopropylethynyl)-  
21 1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one. Its molecular formula is  
22  $C_{14}H_9ClF_3NO_2$  and its structural formula is:



23  
24 Efavirenz is a white to slightly pink crystalline powder with a molecular mass of 315.68.  
25 It is practically insoluble in water (<10  $\mu\text{g/mL}$ ).

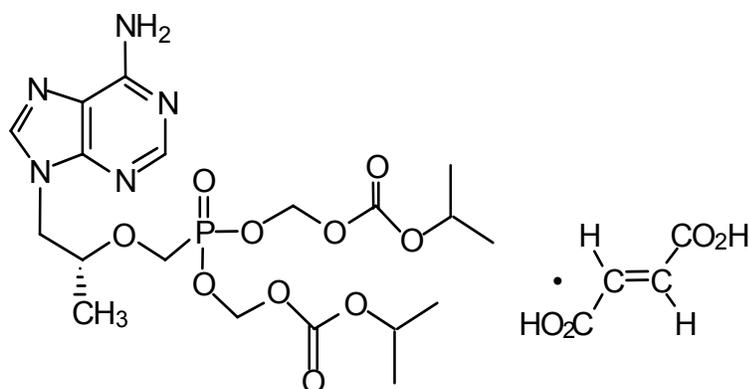
26 **Emtricitabine:** The chemical name of emtricitabine is 5-fluoro-1-(2*R*,5*S*)-[2-  
27 (hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. Emtricitabine is the (-) enantiomer of a  
28 thio analog of cytidine, which differs from other cytidine analogs in that it has a fluorine  
29 in the 5-position.

30 It has a molecular formula of  $C_8H_{10}FN_3O_3S$  and a molecular weight of 247.24. It has the  
31 following structural formula:



32  
33 Emtricitabine is a white to off-white crystalline powder with a solubility of approximately  
34 112 mg/mL in water at 25 °C.

35 **Tenofovir disoproxil fumarate:** Tenofovir DF is a fumaric acid salt of the *bis*-  
36 isopropoxycarbonyloxymethyl ester derivative of tenofovir. The chemical name of  
37 tenofovir disoproxil fumarate is 9-[(*R*)-2[[bis[[isopropoxycarbonyloxy]-  
38 methoxy]phosphinyl]methoxy]propyl]adenine fumarate (1:1). It has a molecular formula  
39 of  $C_{19}H_{30}N_5O_{10}P \cdot C_4H_4O_4$  and a molecular weight of 635.52. It has the following  
40 structural formula:



41  
 42 Tenofovir DF is a white to off-white crystalline powder with a solubility of 13.4 mg/mL in  
 43 water at 25 °C.

#### 44 **MICROBIOLOGY**

45 For additional information on Mechanism of Action, Antiviral Activity, Resistance and  
 46 Cross Resistance, please consult the SUSTIVA, EMTRIVA and VIREAD prescribing  
 47 information.

#### 48 **Mechanism of Action**

49 **Efavirenz:** Efavirenz is a non-nucleoside reverse transcriptase inhibitor of HIV-1.  
 50 Efavirenz activity is mediated predominantly by noncompetitive inhibition of HIV-1  
 51 reverse transcriptase (RT). HIV-2 RT and human cellular DNA polymerases  $\alpha$ ,  $\beta$ ,  $\gamma$ ,  
 52 and  $\delta$  are not inhibited by efavirenz.

53 **Emtricitabine:** Emtricitabine, a synthetic nucleoside analog of cytidine, is  
 54 phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine  
 55 5'-triphosphate inhibits the activity of the HIV-1 RT by competing with the natural  
 56 substrate deoxycytidine 5'-triphosphate and by being incorporated into nascent viral  
 57 DNA which results in chain termination. Emtricitabine 5'-triphosphate is a weak inhibitor  
 58 of mammalian DNA polymerase  $\alpha$ ,  $\beta$ ,  $\epsilon$ , and mitochondrial DNA polymerase  $\gamma$ .

59 **Tenofovir disoproxil fumarate:** Tenofovir DF is an acyclic nucleoside phosphonate  
 60 diester analog of adenosine monophosphate. Tenofovir DF requires initial diester  
 61 hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular  
 62 enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of  
 63 HIV-1 RT by competing with the natural substrate deoxyadenosine 5'-triphosphate and,  
 64 after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a  
 65 weak inhibitor of mammalian DNA polymerases  $\alpha$ ,  $\beta$ , and mitochondrial DNA  
 66 polymerase  $\gamma$ .

#### 67 **Antiviral Activity**

68 **Efavirenz, emtricitabine, and tenofovir disoproxil fumarate:** In combination studies  
 69 evaluating the antiviral activity in cell culture of emtricitabine and efavirenz together,  
 70 efavirenz and tenofovir together, and emtricitabine and tenofovir together, additive to  
 71 synergistic antiviral effects were observed.

72 **Efavirenz:** The concentration of efavirenz inhibiting replication of wild-type laboratory  
 73 adapted strains and clinical isolates in cell culture by 90–95% ( $EC_{90-95}$ ) ranged from

74 1.7–25 nM in lymphoblastoid cell lines, peripheral blood mononuclear cells, and  
75 macrophage/monocyte cultures. Efavirenz demonstrated additive antiviral activity  
76 against HIV-1 in cell culture when combined with non-nucleoside reverse transcriptase  
77 inhibitors (NNRTIs) (delavirdine and nevirapine), nucleoside reverse transcriptase  
78 inhibitors (NRTIs) (abacavir, didanosine, lamivudine, stavudine, zalcitabine, and  
79 zidovudine), protease inhibitors (PIs) (amprenavir, indinavir, lopinavir, nelfinavir,  
80 ritonavir, and saquinavir), and the fusion inhibitor enfuvirtide. Efavirenz demonstrated  
81 additive to antagonistic antiviral activity in cell culture with atazanavir. Efavirenz  
82 demonstrated antiviral activity against most non-clade B isolates (subtypes A, AE, AG,  
83 C, D, F, G, J, and N), but had reduced antiviral activity against group O viruses.  
84 Efavirenz is not active against HIV-2.

85 **Emtricitabine:** The antiviral activity in cell culture of emtricitabine against laboratory  
86 and clinical isolates of HIV was assessed in lymphoblastoid cell lines, the MAGI-CCR5  
87 cell line, and peripheral blood mononuclear cells. The 50% effective concentration  
88 ( $EC_{50}$ ) values for emtricitabine were in the range of 0.0013–0.64  $\mu$ M (0.0003–0.158  
89  $\mu$ g/mL). In drug combination studies of emtricitabine with NRTIs (abacavir, lamivudine,  
90 stavudine, zalcitabine, and zidovudine), NNRTIs (delavirdine, efavirenz, and  
91 nevirapine), and PIs (amprenavir, nelfinavir, ritonavir, and saquinavir), additive to  
92 synergistic effects were observed. Emtricitabine displayed antiviral activity in cell  
93 culture against HIV-1 clades A, B, C, D, E, F, and G ( $EC_{50}$  values ranged from 0.007–  
94 0.075  $\mu$ M) and showed strain specific activity against HIV-2 ( $EC_{50}$  values ranged from  
95 0.007–1.5  $\mu$ M).

96 **Tenofovir disoproxil fumarate:** The antiviral activity in cell culture of tenofovir against  
97 laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines,  
98 primary monocyte/macrophage cells and peripheral blood lymphocytes. The  $EC_{50}$   
99 values for tenofovir were in the range of 0.04–8.5  $\mu$ M. In drug combination studies of  
100 tenofovir with NRTIs (abacavir, didanosine, lamivudine, stavudine, zalcitabine, and  
101 zidovudine), NNRTIs (delavirdine, efavirenz, and nevirapine), and PIs (amprenavir,  
102 indinavir, nelfinavir, ritonavir, and saquinavir), additive to synergistic effects were  
103 observed. Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B,  
104 C, D, E, F, G and O ( $EC_{50}$  values ranged from 0.5–2.2  $\mu$ M) and showed strain specific  
105 activity against HIV-2 ( $EC_{50}$  values ranged from 1.6  $\mu$ M to 4.9  $\mu$ M).

## 106 **Resistance**

107 **Efavirenz, emtricitabine, and tenofovir disoproxil fumarate:** HIV-1 isolates with  
108 reduced susceptibility to the combination of emtricitabine and tenofovir have been  
109 selected in cell culture and in clinical studies. Genotypic analysis of these isolates  
110 identified the M184V/I and/or K65R amino acid substitutions in the viral RT.

111 In a clinical study of treatment-naïve patients (Study 934, **INDICATION AND USAGE,**  
112 **see Description of Clinical Studies**) resistance analysis was performed on HIV  
113 isolates from all virologic failure patients with >400 copies/mL of HIV-1 RNA at Week 48  
114 or early discontinuations. Genotypic resistance to efavirenz, predominantly the K103N  
115 substitution, was the most common form of resistance that developed. Resistance to  
116 efavirenz occurred in 9/12 (75%) analyzed patients in the emtricitabine + tenofovir DF  
117 group and in 16/22 (73%) analyzed patients in the zidovudine/lamivudine fixed-dose  
118 combination group. The M184V amino acid substitution, associated with resistance to

119 emtricitabine and lamivudine, was observed in 2/12 (17%) analyzed patient isolates in  
120 the emtricitabine + tenofovir DF group and in 7/22 (32%) analyzed patient isolates in the  
121 zidovudine/lamivudine group. Through 48 weeks of Study 934, no patients developed a  
122 detectable K65R mutation in their HIV as analyzed through standard genotypic analysis.  
123 Insufficient data are available to assess the development of the K65R mutation upon  
124 prolonged exposure to this regimen.

125 In a clinical study of treatment-naïve patients, isolates from 8 of 47 patients receiving  
126 tenofovir DF developed the K65R substitution through 144 weeks of therapy; 7 of these  
127 occurred in the first 48 weeks of treatment and one at Week 96. In treatment  
128 experienced patients, 14/304 (5%) of tenofovir DF treated patients with virologic failure  
129 through Week 96 showed >1.4 fold (median 2.7) reduced susceptibility to tenofovir.  
130 Genotypic analysis of the resistant isolates showed a mutation in the HIV-1 RT gene  
131 resulting in the K65R amino acid substitution.

132 **Efavirenz:** Clinical isolates with reduced susceptibility in cell culture to efavirenz have  
133 been obtained. The most frequently observed amino acid substitution in clinical studies  
134 with efavirenz is K103N (54%). One or more RT substitutions at amino acid positions  
135 98, 100, 101, 103, 106, 108, 188, 190, 225, 227, and 230 were observed in patients  
136 failing treatment with efavirenz in combination with other antiretrovirals. Other  
137 resistance mutations observed to emerge commonly included L100I (7%), K101E/Q/R  
138 (14%), V108I (11%), G190S/T/A (7%), P225H (18%), and M230I/L (11%).

139 HIV-1 isolates with reduced susceptibility to efavirenz (>380-fold increase in EC<sub>90</sub> value)  
140 emerged rapidly under selection in cell culture. Genotypic characterization of these  
141 viruses identified mutations resulting in single amino acid substitutions L100I or V179D,  
142 double substitutions L100I/V108I, and triple substitutions L100I/V179D/Y181C in RT.

143 **Emtricitabine:** Emtricitabine-resistant isolates of HIV have been selected in cell culture  
144 and in clinical studies. Genotypic analysis of these isolates showed that the reduced  
145 susceptibility to emtricitabine was associated with a mutation in the HIV RT gene at  
146 codon 184 which resulted in an amino acid substitution of methionine by valine or  
147 isoleucine (M184V/I).

148 **Tenofovir disoproxil fumarate:** HIV-1 isolates with reduced susceptibility to tenofovir  
149 have been selected in cell culture. These viruses expressed a K65R mutation in RT  
150 and showed a 2–4 fold reduction in susceptibility to tenofovir.

## 151 **Cross-resistance**

152 **Efavirenz, emtricitabine, and tenofovir disoproxil fumarate:** Cross-resistance has  
153 been recognized among NNRTIs. Cross resistance has also been recognized among  
154 certain NRTIs. The M184V/I and/or K65R substitutions selected in cell culture by the  
155 combination of emtricitabine and tenofovir are also observed in some HIV-1 isolates  
156 from subjects failing treatment with tenofovir in combination with either lamivudine or  
157 emtricitabine, and either abacavir or didanosine. Therefore, cross-resistance among  
158 these drugs may occur in patients whose virus harbors either or both of these amino  
159 acid substitutions.

160 **Efavirenz:** Clinical isolates previously characterized as efavirenz-resistant were also  
161 phenotypically resistant in cell culture to delavirdine and nevirapine compared to  
162 baseline. Delavirdine- and/or nevirapine-resistant clinical viral isolates with NNRTI

163 resistance-associated substitutions (A98G, L100I, K101E/P, K103N/S, V106A, Y181X,  
164 Y188X, G190X, P225H, F227L, or M230L) showed reduced susceptibility to efavirenz in  
165 cell culture. Greater than 90% of NRTI-resistant isolates tested in cell culture retained  
166 susceptibility to efavirenz.

167 **Emtricitabine:** Emtricitabine-resistant isolates (M184V/I) were cross-resistant to  
168 lamivudine and zalcitabine but retained susceptibility in cell culture to didanosine,  
169 stavudine, tenofovir, zidovudine, and NNRTIs (delavirdine, efavirenz, and nevirapine).  
170 HIV-1 isolates containing the K65R substitution, selected in vivo by abacavir,  
171 didanosine, tenofovir, and zalcitabine, demonstrated reduced susceptibility to inhibition  
172 by emtricitabine. Viruses harboring mutations conferring reduced susceptibility to  
173 stavudine and zidovudine (M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E) or  
174 didanosine (L74V) remained sensitive to emtricitabine.

175 **Tenofovir disoproxil fumarate:** The K65R mutation selected by tenofovir is also  
176 selected in some HIV-1 infected patients treated with abacavir, didanosine, or  
177 zalcitabine. HIV-1 isolates with the K65R mutation also showed reduced susceptibility  
178 to emtricitabine and lamivudine. Therefore, cross-resistance among these drugs may  
179 occur in patients whose virus harbors the K65R mutation. HIV-1 isolates from patients  
180 (N=20) whose HIV-1 expressed a mean of 3 zidovudine-associated RT amino acid  
181 substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N) showed a 3.1-fold  
182 decrease in the susceptibility to tenofovir. Multinucleoside resistant HIV-1 with a T69S  
183 double insertion mutation in the RT showed reduced susceptibility to tenofovir.

## 184 **CLINICAL PHARMACOLOGY**

### 185 **Pharmacokinetics in Adults**

186 **ATRIPLA:** One ATRIPLA Tablet is bioequivalent to one SUSTIVA Tablet (600 mg) plus  
187 one EMTRIVA Capsule (200 mg) plus one VIREAD Tablet (300 mg) following single-  
188 dose administration to fasting healthy subjects (N=45).

189 **Efavirenz:** In HIV-infected patients time-to-peak plasma concentrations were  
190 approximately 3–5 hours and steady-state plasma concentrations were reached in 6–10  
191 days. In 35 patients receiving efavirenz 600 mg once daily, steady-state  $C_{max}$  was  $12.9$   
192  $\pm 3.7$   $\mu\text{M}$  (mean  $\pm$  SD),  $C_{min}$  was  $5.6 \pm 3.2$   $\mu\text{M}$ , and AUC was  $184 \pm 73$   $\mu\text{M}\cdot\text{hr}$ . Efavirenz  
193 is highly bound (approximately 99.5–99.75%) to human plasma proteins, predominantly  
194 albumin. Following administration of  $^{14}\text{C}$ -labeled efavirenz, 14–34% of the dose was  
195 recovered in the urine (mostly as metabolites) and 16–61% was recovered in feces  
196 (mostly as parent drug). In vitro studies suggest CYP3A4 and CYP2B6 are the major  
197 isozymes responsible for efavirenz metabolism. Efavirenz has been shown to induce  
198 P450 enzymes, resulting in induction of its own metabolism. Efavirenz has a terminal  
199 half-life of 52–76 hours after single doses and 40–55 hours after multiple doses.

200 **Emtricitabine:** Following oral administration, emtricitabine is rapidly absorbed with  
201 peak plasma concentrations occurring at 1–2 hours post-dose. Following multiple dose  
202 oral administration of emtricitabine to 20 HIV-infected subjects, the steady-state plasma  
203 emtricitabine  $C_{max}$  was  $1.8 \pm 0.7$   $\mu\text{g}/\text{mL}$  (mean  $\pm$  SD) and the AUC over a 24-hour  
204 dosing interval was  $10.0 \pm 3.1$   $\mu\text{g}\cdot\text{hr}/\text{mL}$ . The mean steady state plasma trough  
205 concentration at 24 hours post-dose was  $0.09$   $\mu\text{g}/\text{mL}$ . The mean absolute bioavailability  
206 of emtricitabine was 93%. In vitro binding of emtricitabine to human plasma proteins is

207 <4% and is independent of concentration over the range of 0.02–200 µg/mL. Following  
208 administration of radiolabelled emtricitabine, approximately 86% is recovered in the  
209 urine and 13% is recovered as metabolites. The metabolites of emtricitabine include  
210 3'-sulfoxide diastereomers and their glucuronic acid conjugate. Emtricitabine is  
211 eliminated by a combination of glomerular filtration and active tubular secretion with a  
212 renal clearance in adults with normal renal function of 213 ± 89 mL/min (mean ± SD).  
213 Following a single oral dose, the plasma emtricitabine half-life is approximately 10  
214 hours.

215 **Tenofovir disoproxil fumarate:** Following oral administration of a single 300 mg dose  
216 of tenofovir DF to HIV-1 infected patients in the fasted state, maximum serum  
217 concentrations ( $C_{max}$ ) were achieved in 1.0 ± 0.4 hrs (mean ± SD) and  $C_{max}$  and AUC  
218 values were 296 ± 90 ng/mL and 2287 ± 685 ng•hr/mL, respectively. The oral  
219 bioavailability of tenofovir from tenofovir DF in fasted patients is approximately 25%. In  
220 vitro binding of tenofovir to human plasma proteins is <0.7% and is independent of  
221 concentration over the range of 0.01–25 µg/mL. Approximately 70–80% of the  
222 intravenous dose of tenofovir is recovered as unchanged drug in the urine. Tenofovir is  
223 eliminated by a combination of glomerular filtration and active tubular secretion with a  
224 renal clearance in adults with normal renal function of 243 ± 33 mL/min (mean ± SD).  
225 Following a single oral dose, the terminal elimination half-life of tenofovir is  
226 approximately 17 hours.

## 227 **Effects of Food on Oral Absorption**

228 ATRIPLA has not been evaluated in the presence of food. Administration of efavirenz  
229 tablets with a high fat meal increased the mean AUC and  $C_{max}$  of efavirenz by 28% and  
230 79%, respectively, compared to administration in the fasted state. Compared to fasted  
231 administration, dosing of tenofovir DF and emtricitabine in combination with either a  
232 high fat meal or a light meal increased the mean AUC and  $C_{max}$  of tenofovir by 35% and  
233 15%, respectively, without affecting emtricitabine exposures (**see DOSAGE AND**  
234 **ADMINISTRATION and PRECAUTIONS, Information for Patients**).

## 235 **Special Populations**

### 236 **Race**

237 **Efavirenz:** The pharmacokinetics of efavirenz in patients appear to be similar among  
238 the racial groups studied.

239 **Emtricitabine:** No pharmacokinetic differences due to race have been identified  
240 following the administration of emtricitabine.

241 **Tenofovir disoproxil fumarate:** There were insufficient numbers from racial and  
242 ethnic groups other than Caucasian to adequately determine potential pharmacokinetic  
243 differences among these populations following the administration of tenofovir DF.

### 244 **Gender**

245 **Efavirenz, emtricitabine, and tenofovir disoproxil fumarate:** Efavirenz,  
246 emtricitabine, and tenofovir pharmacokinetics are similar in male and female patients.

### 247 **Pediatric and Geriatric Patients**

248 Pharmacokinetic studies of tenofovir DF have not been performed in pediatric patients  
249 (<18 years). Efavirenz has not been studied in pediatric patients below 3 years of age  
250 or who weigh less than 13 kg. Emtricitabine has been studied in pediatric patients from  
251 3 months to 17 years of age. ATRIPLA is not recommended for pediatric  
252 administration. Pharmacokinetics of efavirenz, emtricitabine and tenofovir have not  
253 been fully evaluated in the elderly (>65 years) (**see PRECAUTIONS, Pediatric Use,**  
254 **Geriatric Use**).

#### 255 **Patients with Impaired Renal Function**

256 **Efavirenz:** The pharmacokinetics of efavirenz have not been studied in patients with  
257 renal insufficiency; however, less than 1% of efavirenz is excreted unchanged in the  
258 urine, so the impact of renal impairment on efavirenz elimination should be minimal.

259 **Emtricitabine and tenofovir disoproxil fumarate:** The pharmacokinetics of  
260 emtricitabine and tenofovir DF are altered in patients with renal impairment. In patients  
261 with creatinine clearance <50 mL/min,  $C_{max}$  and  $AUC_{0-\infty}$  of emtricitabine and tenofovir  
262 were increased (**see WARNINGS, Renal Impairment**).

#### 263 **Patients with Hepatic Impairment**

264 **Efavirenz:** The pharmacokinetics of efavirenz have not been adequately studied in  
265 patients with hepatic impairment (**see PRECAUTIONS, Liver Enzymes**).

266 **Emtricitabine:** The pharmacokinetics of emtricitabine have not been studied in  
267 patients with hepatic impairment; however, emtricitabine is not significantly metabolized  
268 by liver enzymes, so the impact of liver impairment should be limited.

269 **Tenofovir disoproxil fumarate:** The pharmacokinetics of tenofovir following a 300 mg  
270 dose of tenofovir DF have been studied in non-HIV infected patients with moderate to  
271 severe hepatic impairment. There were no substantial alterations in tenofovir  
272 pharmacokinetics in patients with hepatic impairment compared with unimpaired  
273 patients.

274 **Pregnancy (see WARNINGS, Reproductive Risk Potential)**

275 **Nursing Mothers (see PRECAUTIONS, Nursing Mothers)**

276 **Drug Interactions (see CONTRAINDICATIONS and PRECAUTIONS, Drug**  
277 **Interactions)**

278 **ATRIPLA:** The drug interactions described are based on studies conducted with  
279 efavirenz, emtricitabine, or tenofovir DF as individual agents; no drug interaction studies  
280 have been conducted using ATRIPLA.

281 **Efavirenz:** The steady-state pharmacokinetics of efavirenz and tenofovir were  
282 unaffected when efavirenz and tenofovir DF were administered together versus each  
283 agent dosed alone. Specific drug interaction studies have not been performed with  
284 efavirenz and NRTIs other than tenofovir, lamivudine, and zidovudine. Clinically  
285 significant interactions would not be expected based on NRTIs elimination pathways.

286 Efavirenz has been shown in vivo to cause hepatic enzyme induction, thus increasing  
287 the biotransformation of some drugs metabolized by CYP3A4. In vitro studies have  
288 shown that efavirenz inhibited P450 isozymes 2C9, 2C19, and 3A4 with  $K_i$  values  
289 (8.5–17  $\mu$ M) in the range of observed efavirenz plasma concentrations. In in vitro

290 studies, efavirenz did not inhibit CYP2E1 and inhibited CYP2D6 and CYP1A2 ( $K_i$  values  
291 82–160  $\mu\text{M}$ ) only at concentrations well above those achieved clinically.

292 Coadministration of efavirenz with drugs primarily metabolized by 2C9, 2C19, and 3A4  
293 isozymes may result in altered plasma concentrations of the coadministered drug.

294 Drugs which induce CYP3A4 activity would be expected to increase the clearance of  
295 efavirenz resulting in lowered plasma concentrations.

296 Drug interaction studies were performed with efavirenz and other drugs likely to be  
297 coadministered or drugs commonly used as probes for pharmacokinetic interaction.

298 There was no clinically significant interaction observed between efavirenz and  
299 zidovudine, lamivudine, azithromycin, fluconazole, lorazepam, cetirizine, or paroxetine.

300 Single doses of famotidine or an aluminum and magnesium antacid with simethicone  
301 had no effects on efavirenz exposures. The effects of coadministration of efavirenz on

302  $C_{\text{max}}$ , AUC, and  $C_{\text{min}}$  are summarized in Table 1 (effect of other drugs on efavirenz) and  
303 Table 2 (effect of efavirenz on other drugs). For information regarding clinical

304 recommendations **see PRECAUTIONS, Drug Interactions.**

305

**Table 1 Drug Interactions: Changes in Pharmacokinetic Parameters for Efavirenz in the Presence of the Coadministered Drug**

				Mean % Change of Efavirenz Pharmacokinetic Parameters <sup>1</sup> (90% CI)		
Coadministered Drug	Dose of Coadministered Drug (mg)	Efavirenz Dose (mg)	N	C <sub>max</sub>	AUC	C <sub>min</sub>
Indinavir	800 mg q8h × 14 days	200 mg × 14 days	11	↔	↔	↔
Lopinavir/ritonavir	400/100 mg q12h × 9 days	600 mg × 9 days	11, 12 <sup>2</sup>	↔	↓ 16 (↓ 38 to ↑ 15)	↓ 16 (↓ 42 to ↑ 20)
Nelfinavir	750 mg q8h × 7 days	600 mg × 7 days	10	↓ 12 (↓ 32 to ↑ 13) <sup>3</sup>	↓ 12 (↓ 35 to ↑ 18) <sup>3</sup>	↓ 21 (↓ 53 to ↑ 33)
Ritonavir	500 mg q12h × 8 days	600 mg × 10 days	9	↑ 14 (↑ 4 to ↑ 26)	↑ 21 (↑ 10 to ↑ 34)	↑ 25 (↑ 7 to ↑ 46) <sup>3</sup>
Saquinavir SGC <sup>4</sup>	1200 mg q8h × 10 days	600 mg × 10 days	13	↓ 13 (↓ 5 to ↓ 20)	↓ 12 (↓ 4 to ↓ 19)	↓ 14 (↓ 2 to ↓ 24) <sup>3</sup>
Clarithromycin	500 mg q12h × 7 days	400 mg × 7 days	12	↑ 11 (↑ 3 to ↑ 19)	↔	↔
Itraconazole	200 mg q12h × 14 days	600 mg × 28 days	16	↔	↔	↔
Rifabutin	300 mg qd × 14 days	600 mg × 14 days	11	↔	↔	↓ 12 (↓ 24 to ↑ 1)
Rifampin	600 mg × 7 days	600 mg × 7 days	12	↓ 20 (↓ 11 to ↓ 28)	↓ 26 (↓ 15 to ↓ 36)	↓ 32 (↓ 15 to ↓ 46)
Atorvastatin	10 mg qd × 4 days	600 mg × 15 days	14	↔	↔	↔
Pravastatin	40 mg qd × 4 days	600 mg × 15 days	11	↔	↔	↔
Simvastatin	40 mg qd × 4 days	600 mg × 15 days	14	↓ 12 (↓ 28 to ↑ 8)	↔	↓ 12 (↓ 25 to ↑ 3)
Carbamazepine	200 mg qd × 3 days, 200 mg bid × 3 days, then 400 mg qd × 15 days	600 mg × 35 days	14	↓ 21 (↓ 15 to ↓ 26)	↓ 36 (↓ 32 to ↓ 40)	↓ 47 (↓ 41 to ↓ 53)
Diltiazem	240 mg × 14 days	600 mg × 28 days	12	↑ 16 (↑ 6 to ↑ 26)	↑ 11 (↑ 5 to ↑ 18)	↑ 13 (↑ 1 to ↑ 26)
Ethinyl estradiol	50 µg single dose	400 mg × 10 days	13	↔	↔	↔

				Mean % Change of Efavirenz Pharmacokinetic Parameters <sup>1</sup> (90% CI)		
Coadministered Drug	Dose of Coadministered Drug (mg)	Efavirenz Dose (mg)	N	C <sub>max</sub>	AUC	C <sub>min</sub>
Sertraline	50 mg qd × 14 days	600 mg × 14 days	13	↑ 11 (↑ 6 to ↑ 16)	↔	↔
Voriconazole	400 mg po q12h × 1 day then 200 mg po q12h × 8 days	400 mg × 9 days	NA	↑ 38 <sup>5</sup>	↑ 44 <sup>5</sup>	NA
	300 mg po q12h days 2-7	300 mg × 7 days	NA	↓ 14 <sup>6</sup> (↓ 7 to ↓ 21)	↔ <sup>6</sup>	NA
	400 mg po q12h days 2-7	300 mg × 7 days	NA	↔ <sup>6</sup>	↑ 17 <sup>6</sup> (↑ 6 to ↑ 29)	NA

- 308 1. Increase = ↑; Decrease = ↓; No Effect = ↔  
309 2. Parallel-group design; N for efavirenz + lopinavir/ritonavir, N for efavirenz alone.  
310 3. 95% CI  
311 4. Soft Gelatin Capsule  
312 5. 90% CI not available  
313 6. Relative to steady-state administration of efavirenz (600 mg once daily for 9 days).  
314 NA = not available

315 **Table 2 Drug Interactions: Changes in Pharmacokinetic Parameters for**  
316 **Coadministered Drug in the Presence of Efavirenz**

				Mean % Change of Coadministered Drug Pharmacokinetic Parameters <sup>1</sup> (90% CI)		
Coadministered Drug	Dose of Coadministered Drug (mg)	Efavirenz Dose (mg)	N	C <sub>max</sub>	AUC	C <sub>min</sub>
Atazanavir	400 mg qd with a light meal d 1–20	600 mg qd with a light meal d 7–20	27	↓ 59 (↓ 49 to ↓ 67)	↓ 74 (↓ 68 to ↓ 78)	↓ 93 (↓ 90 to ↓ 95)
	400 mg qd d 1–6, then 300 mg qd d 7–20 with ritonavir 100 mg qd and a light meal	600 mg qd 2 h after atazanavir and ritonavir d 7–20	13	↑ 14 <sup>2</sup> (↓ 17 to ↑ 58)	↑ 39 <sup>2</sup> (↑ 2 to ↑ 88)	↑ 48 <sup>2</sup> (↑ 24 to ↑ 76)
Indinavir	1000 mg q8h × 10 days	600 mg × 10 days	20			
	After morning dose			↔ <sup>3</sup>	↓ 33 <sup>3</sup> (↓ 26 to ↓ 39)	↓ 39 <sup>3</sup> (↓ 24 to ↓ 51)
	After afternoon dose			↔ <sup>3</sup>	↓ 37 <sup>3</sup> (↓ 26 to ↓ 46)	↓ 52 <sup>3</sup> (↓ 47 to ↓ 57)

				Mean % Change of Coadministered Drug Pharmacokinetic Parameters <sup>1</sup> (90% CI)		
Coadministered Drug	Dose of Coadministered Drug (mg)	Efavirenz Dose (mg)	N	C <sub>max</sub>	AUC	C <sub>min</sub>
	After evening dose			↓ 29 <sup>3</sup> (↓ 11 to ↓ 43)	↓ 46 <sup>3</sup> (↓ 37 to ↓ 54)	↓ 57 <sup>3</sup> (↓ 50 to ↓ 63)
Lopinavir/ ritonavir	400/100 mg q12h × 9 days	600 mg × 9 days	11, 7 <sup>4</sup>	↔ <sup>5</sup>	↓ 19 <sup>5</sup> (↓ 36 to ↑ 3)	↓ 39 <sup>5</sup> (↓ 3 to ↓ 62)
Nelfinavir  Metabolite AG-1402	750 mg q8h × 7 days	600 mg × 7 days	10	↑ 21 (↑ 10 to ↑ 33)  ↓ 40 (↓ 30 to ↓ 48)	↑ 20 (↑ 8 to ↑ 34)  ↓ 37 (↓ 25 to ↓ 48)	↔  ↓ 43 (↓ 21 to ↓ 59)
Ritonavir	500 mg q12h × 8 days	600 mg × 10 days	11			
	After AM dose			↑ 24 (↑ 12 to ↑ 38)	↑ 18 (↑ 6 to ↑ 33)	↑ 42 (↑ 9 to ↑ 86) <sup>6</sup>
	After PM dose			↔	↔	↑ 24 (↑ 3 to ↑ 50) <sup>6</sup>
Saquinavir SGC <sup>7</sup>	1200 mg q8h × 10 days	600 mg × 10 days	12	↓ 50 (↓ 28 to ↓ 66)	↓ 62 (↓ 45 to ↓ 74)	↓ 56 (↓ 16 to ↓ 77) <sup>6</sup>

				Mean % Change of Coadministered Drug Pharmacokinetic Parameters <sup>1</sup> (90% CI)		
Coadministered Drug	Dose of Coadministered Drug (mg)	Efavirenz Dose (mg)	N	C <sub>max</sub>	AUC	C <sub>min</sub>
Clarithromycin  14-OH metabolite	500 mg q12h × 7 days	400 mg × 7 days	11	↓ 26 (↓ 15 to ↓ 35)  ↑ 49 (↑ 32 to ↑ 69)	↓ 39 (↓ 30 to ↓ 46)  ↑ 34 (↑ 18 to ↑ 53)	↓ 53 (↓ 42 to ↓ 63)  ↑ 26 (↑ 9 to ↑ 45)
Itraconazole  Hydroxy-itraconazole	200 mg q12h × 28 days	600 mg × 14 days	18	↓ 37 (↓ 20 to ↓ 51)  ↓ 35 (↓ 12 to ↓ 52)	↓ 39 (↓ 21 to ↓ 53)  ↓ 37 (↓ 14 to ↓ 55)	↓ 44 (↓ 27 to ↓ 58)  ↓ 43 (↓ 18 to ↓ 60)
Rifabutin	300 mg qd × 14 days	600 mg × 14 days	9	↓ 32 (↓ 15 to ↓ 46)	↓ 38 (↓ 28 to ↓ 47)	↓ 45 (↓ 31 to ↓ 56)
Atorvastatin  Total active (including metabolites)	10 mg qd × 4 days	600 mg × 15 days	14	↓ 14 (↓ 1 to ↓ 26)  ↓ 15 (↓ 2 to ↓ 26)	↓ 43 (↓ 34 to ↓ 50)  ↓ 32 (↓ 21 to ↓ 41)	↓ 69 (↓ 49 to ↓ 81)  ↓ 48 (↓ 23 to ↓ 64)
Pravastatin	40 mg qd × 4 days	600 mg × 15 days	13	↓ 32 (↓ 59 to ↑ 12)	↓ 44 (↓ 26 to ↓ 57)	↓ 19 (↓ 0 to ↓ 35)
Simvastatin  Total active (including metabolites)	40 mg qd × 4 days	600 mg × 15 days	14	↓ 72 (↓ 63 to ↓ 79)  ↓ 68 (↓ 55 to ↓ 78)	↓ 68 (↓ 62 to ↓ 73)  ↓ 60 (↓ 52 to ↓ 68)	↓ 45 (↓ 20 to ↓ 62)  NA <sup>10</sup>
Carbamazepine  Epoxide metabolite	200 mg qd × 3 days, 200 mg bid × 3 days, then 400 mg qd × 29 days	600 mg × 14 days	12	↓ 20 (↓ 15 to ↓ 24)  ↔	↓ 27 (↓ 20 to ↓ 33)  ↔	↓ 35 (↓ 24 to ↓ 44)  ↓ 13 (↓ 30 to ↑ 7)

				Mean % Change of Coadministered Drug Pharmacokinetic Parameters <sup>1</sup> (90% CI)		
Coadministered Drug	Dose of Coadministered Drug (mg)	Efavirenz Dose (mg)	N	C <sub>max</sub>	AUC	C <sub>min</sub>
Diltiazem	240 mg × 21 days	600 mg × 14 days	13	↓ 60 (↓ 50 to ↓ 68)	↓ 69 (↓ 55 to ↓ 79)	↓ 63 (↓ 44 to ↓ 75)
Desacetyl diltiazem				↓ 64 (↓ 57 to ↓ 69)	↓ 75 (↓ 59 to ↓ 84)	↓ 62 (↓ 44 to ↓ 75)
N-monodesmethyl diltiazem				↓ 28 (↓ 7 to ↓ 44)	↓ 37 (↓ 17 to ↓ 52)	(↓ 37 (↓ 17 to ↓ 52)
Ethinyl estradiol	50 µg single dose	400 mg × 10 days	13	↔	↑ 37 (↑ 25 to ↑ 51)	NA
Methadone	Stable maintenance 35–100 mg daily	600 mg × 14–21 days	11	↓ 45 (↓ 25 to ↓ 59)	↓ 52 (↓ 33 to ↓ 66)	NA
Sertraline	50 mg qd × 14 days	600 mg × 14 days	13	↓ 29 (↓ 15 to ↓ 40)	↓ 39 (↓ 27 to ↓ 50)	↓ 46 (↓ 31 to ↓ 58)
Voriconazole	400 mg po q12h × 1 day then 200 mg po q12h × 8 days	400 mg × 9 days	NA	↓ 61 <sup>8</sup>	↓ 77 <sup>8</sup>	NA
	300 mg po q12h days 2-7	300 mg × 7 days	NA	↓ 36 <sup>9</sup> (↓ 21 to ↓ 49)	↓ 55 <sup>9</sup> (↓ 45 to ↓ 62)	NA
	400 mg po q12h days 2-7	300 mg × 7 days	NA	↑ 23 <sup>9</sup> (↓ 1 to ↑ 53)	↓ 7 <sup>9</sup> (↓ 23 to ↑ 13)	NA

- 317 1. Increase = ↑; Decrease = ↓; No Effect = ↔  
318 2. Compared with atazanavir 400 mg qd alone.  
319 3. Comparator dose of indinavir was 800 mg q8h × 10 days.  
320 4. Parallel-group design; N for efavirenz + lopinavir/ritonavir, N for lopinavir/ritonavir alone.  
321 5. Values are for lopinavir. The pharmacokinetics of ritonavir 100 mg q12h are unaffected by concurrent efavirenz.  
322 6. 95% CI  
323 7. Soft Gelatin Capsule  
324 8. 90% CI not available  
325 9. Relative to steady-state administration of voriconazole (400 mg for 1 day, then 200 mg po q12h for 2 days).  
326 10. Not available because of insufficient data.  
327 NA = not available  
328

329 **Emtricitabine and tenofovir disoproxil fumarate:** The steady-state pharmacokinetics  
330 of emtricitabine and tenofovir were unaffected when emtricitabine and tenofovir DF were  
331 administered together versus each agent dosed alone.

332 In vitro and clinical pharmacokinetic drug-drug interaction studies have shown that the  
333 potential for CYP450 mediated interactions involving emtricitabine and tenofovir with  
334 other medicinal products is low.

335 Emtricitabine and tenofovir are primarily excreted by the kidneys by a combination of  
336 glomerular filtration and active tubular secretion. No drug-drug interactions due to  
337 competition for renal excretion have been observed; however, coadministration of  
338 emtricitabine and tenofovir DF with drugs that are eliminated by active tubular secretion  
339 may increase concentrations of emtricitabine, tenofovir, and/or the coadministered drug.

340 Drugs that decrease renal function may increase concentrations of emtricitabine and/or  
341 tenofovir.

342 No clinically significant drug interactions have been observed between emtricitabine and  
343 famciclovir, indinavir, stavudine, tenofovir DF, and zidovudine. Similarly, no clinically  
344 significant drug interactions have been observed between tenofovir DF and abacavir,  
345 adefovir dipivoxil, efavirenz, emtricitabine, indinavir, lamivudine, lopinavir/ritonavir,  
346 methadone, nelfinavir, oral contraceptives, ribavirin and saquinavir/ritonavir in studies  
347 conducted in healthy volunteers.

348 Following multiple dosing to HIV-negative subjects receiving either chronic methadone  
349 maintenance therapy, oral contraceptives, or single doses of ribavirin, steady-state  
350 tenofovir pharmacokinetics were similar to those observed in previous studies,  
351 indicating a lack of clinically significant drug interactions between these agents and  
352 tenofovir DF.

353 The effects of coadministered drugs on the  $C_{max}$ , AUC, and  $C_{min}$  of tenofovir are shown  
354 in Table 3. The effects of coadministration of tenofovir DF on  $C_{max}$ , AUC, and  $C_{min}$  of  
355 coadministered drugs are shown in Tables 4 and 5.

356 **Table 3 Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir in**  
 357 **the Presence of the Coadministered Drug<sup>1,2</sup>**

Coadministered Drug	Dose of Coadministered Drug (mg)	N	Mean % Change of Tenofovir Pharmacokinetic Parameters <sup>3</sup> (90% CI)		
			C <sub>max</sub>	AUC	C <sub>min</sub>
Atazanavir <sup>4</sup>	400 once daily × 14 days	33	↑ 14 (↑ 8 to ↑ 20)	↑ 24 (↑ 21 to ↑ 28)	↑ 22 (↑ 15 to ↑ 30)
Didanosine (enteric-coated)	400 once	25	↔	↔	↔
Didanosine (buffered)	250 or 400 once daily × 7 days	14	↔	↔	↔
Lopinavir/ritonavir	400/100 twice daily × 14 days	24	↔	↑ 32 (↑ 25 to ↑ 38)	↑ 51 (↑ 37 to ↑ 66)

- 358 1. All interaction studies conducted in healthy volunteers.  
 359 2. Patients received tenofovir DF 300 mg once daily.  
 360 3. Increase = ↑; Decrease = ↓; No Effect = ↔  
 361 4. Reyataz Prescribing Information

362 **Table 4 Drug Interactions: Changes in Pharmacokinetic Parameters for**  
 363 **Coadministered Drug in the Presence of Tenofovir Disoproxil Fumarate<sup>1,2</sup>**

Coadministered Drug	Dose of Coadministered Drug (mg)	N	Mean % Change of Coadministered Drug Pharmacokinetic Parameters <sup>3</sup> (90% CI)		
			C <sub>max</sub>	AUC	C <sub>min</sub>
Atazanavir <sup>4</sup>	400 once daily × 14 days	34	↓ 21 (↓ 27 to ↓ 14)	↓ 25 (↓ 30 to ↓ 19)	↓ 40 (↓ 48 to ↓ 32)
	Atazanavir/ritonavir 300/100 once daily × 42 days	10	↓ 28 (↓ 50 to ↑ 5)	↓ 25 <sup>5</sup> (↓ 42 to ↓ 3)	↓ 23 <sup>5</sup> (↓ 46 to ↑ 10)
Lopinavir	Lopinavir/ritonavir 400/100 twice daily × 14 days	24	↔	↔	↔
Ritonavir	Lopinavir/ritonavir 400/100 twice daily × 14 days	24	↔	↔	↔

- 364 1. All interaction studies conducted in healthy volunteers.  
 365 2. Patients received tenofovir DF 300 mg once daily.  
 366 3. Increase = ↑; Decrease = ↓; No Effect = ↔  
 367 4. Reyataz Prescribing Information  
 368 5. In HIV-infected patients, addition of tenofovir DF to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and  
 369 C<sub>min</sub> values of atazanavir that were 2.3- and 4-fold higher than the respective values observed for atazanavir  
 370 400 mg when given alone.

371 Coadministration of tenofovir DF with didanosine results in changes in the  
 372 pharmacokinetics of didanosine that may be of clinical significance. Table 5  
 373 summarizes the effects of tenofovir DF on the pharmacokinetics of didanosine.  
 374 Concomitant dosing of tenofovir DF with didanosine buffered tablets or enteric-coated  
 375 capsules significantly increases the C<sub>max</sub> and AUC of didanosine. When didanosine

376 250 mg enteric-coated capsules were administered with tenofovir DF, systemic  
 377 exposures of didanosine were similar to those seen with the 400 mg enteric-coated  
 378 capsules alone under fasted conditions. The mechanism of this interaction is unknown  
 379 (for didanosine dosing adjustment recommendations, **see Table 8 in PRECAUTIONS,**  
 380 **Drug Interactions**).

381 **Table 5 Drug Interactions: Changes in Pharmacokinetic Parameters for Didanosine**  
 382 **in the Presence of Tenofovir Disoproxil Fumarate<sup>1,2</sup>**

Didanosine Dose (mg)/Method of Administration <sup>3,5</sup>	Tenofovir DF Method of Administration <sup>2,5</sup>	N	Mean % Change (90% CI) vs. Didanosine 400 mg Alone, Fasted <sup>4</sup>	
			C <sub>max</sub>	AUC
<b>Buffered tablets</b>				
400 once daily <sup>6</sup> × 7 days	Fasted 1 hour after didanosine	14	↑ 28 (↑ 11 to ↑ 48)	↑ 44 (↑ 31 to ↑ 59)
<b>Enteric coated capsules</b>				
400 once, fasted	With food, 2 hr after didanosine	26	↑ 48 (↑ 25 to ↑ 76)	↑ 48 (↑ 31 to ↑ 67)
400 once, with food	Simultaneously with didanosine	26	↑ 64 (↑ 41 to ↑ 89)	↑ 60 (↑ 44 to ↑ 79)
250 once, fasted	With food, 2 hr after didanosine	28	↓ 10 (↓ 22 to ↑ 3)	↔
250 once, fasted	Simultaneously with didanosine	28	↔	↑ 14 (0 to ↑ 31)
250 once, with food	Simultaneously with didanosine	28	↓ 29 (↓ 39 to ↓ 18)	↓ 11 (↓ 23 to ↑ 2)

- 383 1. All interaction studies conducted in healthy volunteers.  
 384 2. Patients received tenofovir DF 300 mg once daily.  
 385 3. See PRECAUTIONS regarding use of didanosine with ATRIPLA.  
 386 4. Increase = ↑; Decrease = ↓; No Effect = ↔  
 387 5. Administration with food was with a light meal (~373 kcal, 20% fat).  
 388 6. Includes 4 subjects weighing <60 kg receiving ddl 250 mg.

389 **Efavirenz Assay Interference**

391 Cannabinoid Test Interaction: Efavirenz does not bind to cannabinoid receptors. False-  
 392 positive urine cannabinoid test results have been observed in non-HIV-infected  
 393 volunteers receiving efavirenz when the Microgenics Cedia DAU Multi-Level THC assay  
 394 was used for screening. Negative results were obtained when more specific  
 395 confirmatory testing was performed with gas chromatography/mass spectrometry. For  
 396 more information, please consult the SUSTIVA prescribing information.

397 **INDICATIONS AND USAGE**

398 ATRIPLA is indicated for use alone as a complete regimen or in combination with other  
 399 antiretroviral agents for the treatment of HIV-1 infection in adults.

400 **Description of Clinical Studies**

401 Clinical Study 934 supports the use of ATRIPLA Tablets in antiretroviral treatment-naïve  
 402 HIV-1 infected patients. Additional data in support of the use of ATRIPLA in treatment  
 403 naïve patients can be found in the prescribing information for VIREAD.

404 In antiretroviral treatment-experienced patients, the use of ATRIPLA Tablets may be  
 405 considered for patients with HIV strains that are expected to be susceptible to the  
 406 components of ATRIPLA as assessed by treatment history or by genotypic or  
 407 phenotypic testing (**see MICROBIOLOGY, Drug Resistance and Cross**  
 408 **Resistance**).

409 **Study 934: Emtricitabine + Tenofovir Disoproxil Fumarate + Efavirenz Compared**  
 410 **with Zidovudine/Lamivudine + Efavirenz**

411 Data through 48 weeks are reported for Study 934, a randomized, open-label, active-  
 412 controlled multicenter study comparing emtricitabine + tenofovir DF administered in  
 413 combination with efavirenz versus zidovudine/lamivudine fixed-dose combination  
 414 administered in combination with efavirenz in 511 antiretroviral-naïve patients. Patients  
 415 had a mean age of 38 years (range 18–80), 86% were male, 59% were Caucasian and  
 416 23% were Black. The mean baseline CD4 cell count was 245 cells/mm<sup>3</sup> (range 2–1191)  
 417 and median baseline plasma HIV-1 RNA was 5.01 log<sub>10</sub> copies/mL (range 3.56–6.54).  
 418 Patients were stratified by baseline CD4 count (< or ≥ 200 cells/mm<sup>3</sup>) and 41% had CD4  
 419 cell counts <200 cells/mm<sup>3</sup>. Fifty-one percent (51%) of patients had baseline viral loads  
 420 >100,000 copies/mL. Treatment outcomes through 48 weeks for those patients who did  
 421 not have efavirenz resistance at baseline (n=487) are presented in Table 6.

422 **Table 6 Outcomes of Randomized Treatment at Week 48 (Study 934)**

Outcome at Week 48	FTC + TDF + EFV (N=244)	AZT/3TC + EFV (N=243)
	%	%
Responder <sup>1</sup>	84%	73%
Virologic failure <sup>2</sup>	2%	4%
Rebound	1%	3%
Never suppressed through week 48	0%	0%
Change in antiretroviral regimen	1%	1%
Death	<1%	1%
Discontinued due to adverse event	4%	9%
Discontinued for other reasons <sup>3</sup>	10%	14%

- 423 1. Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Week 48.  
 424 2. Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Week 48.  
 425 3. Includes lost to follow-up, patient withdrawal, noncompliance, protocol violation and other reasons.

426 The difference in the proportion of patients who achieved and maintained HIV-1 RNA  
 427 <400 copies/mL through 48 weeks largely results from the higher number of  
 428 discontinuations due to adverse events and other reasons in the zidovudine/lamivudine  
 429 group in this open-label study. In addition, 80% and 70% of patients in the emtricitabine

430 + tenofovir DF and the zidovudine/lamivudine group, respectively, achieved and  
431 maintained HIV-1 RNA <50 copies/mL. The mean increase from baseline in CD4 cell  
432 count was 190 cells/mm<sup>3</sup> in the emtricitabine + tenofovir DF group, and 158 cells/mm<sup>3</sup>  
433 for the zidovudine/lamivudine group.

434 Through 48 weeks, 7 patients in the emtricitabine + tenofovir DF group and 5 patients in  
435 the zidovudine/lamivudine group experienced a new CDC Class C event.

#### 436 **CONTRAINDICATIONS**

437 ATRIPLA is contraindicated in patients with previously demonstrated hypersensitivity to  
438 any of the components of the product.

439  
440 ATRIPLA should not be administered concurrently with astemizole, bepridil, cisapride,  
441 midazolam, pimozide, triazolam or ergot derivatives because competition for CYP3A4  
442 by efavirenz could result in inhibition of metabolism of these drugs and create the  
443 potential for serious and/or life-threatening adverse events (eg, cardiac arrhythmias,  
444 prolonged sedation, or respiratory depression). ATRIPLA should not be administered  
445 concurrently with voriconazole because efavirenz significantly decreases voriconazole  
446 plasma concentrations (**see CLINICAL PHARMACOLOGY and PRECAUTIONS, Drug**  
447 **Interactions**).

#### 448 **WARNINGS**

##### 449 **Lactic Acidosis/Severe Hepatomegaly with Steatosis**

450 Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have  
451 been reported with the use of nucleoside analogs alone or in combination with other  
452 antiretrovirals. A majority of these cases have been in women. Obesity and prolonged  
453 nucleoside exposure may be risk factors. Particular caution should be exercised when  
454 administering nucleoside analogs to any patient with known risk factors for liver disease;  
455 however, cases have also been reported in patients with no known risk factors.  
456 Treatment with ATRIPLA should be suspended in any patient who develops clinical or  
457 laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which  
458 may include hepatomegaly and steatosis even in the absence of marked transaminase  
459 elevations).

##### 460 **Patients Coinfected with HIV and HBV**

461 It is recommended that all patients with HIV be tested for the presence of chronic HBV  
462 before initiating antiretroviral therapy. ATRIPLA is not approved for the treatment of  
463 chronic HBV infection and the safety and efficacy of ATRIPLA have not been  
464 established in patients co-infected with HBV and HIV. Severe acute exacerbations of  
465 hepatitis B have been reported in patients who are coinfecting with HBV and HIV and  
466 have discontinued EMTRIVA or VIREAD. In some of these patients treated with  
467 EMTRIVA, the exacerbations of hepatitis B were associated with liver decompensation  
468 and liver failure. Hepatic function should be monitored closely with both clinical and  
469 laboratory follow up for at least several months in patients who are coinfecting with HIV  
470 and HBV and discontinue ATRIPLA. If appropriate, initiation of anti-hepatitis B therapy  
471 may be warranted.

472 **ALERT: Find out about medicines that should NOT be taken with ATRIPLA.** This  
473 statement is also included on the product's bottle labels (see **CONTRAINDICATIONS**  
474 **and PRECAUTIONS, Drug Interactions**).

#### 475 **Coadministration with Related Drugs**

476 Related drugs not for coadministration with ATRIPLA include EMTRIVA (emtricitabine),  
477 VIREAD (tenofovir DF), TRUVADA (emtricitabine/tenofovir DF), and SUSTIVA  
478 (efavirenz), which contain the same active components as ATRIPLA. Due to similarities  
479 between emtricitabine and lamivudine, ATRIPLA should not be coadministered with  
480 drugs containing lamivudine, including Combivir (lamivudine/zidovudine), Epivir or  
481 Epivir-HBV (lamivudine), Epzicom (abacavir sulfate/lamivudine), or Trizivir (abacavir  
482 sulfate/lamivudine/zidovudine).

#### 483 **Drug Interactions (see CONTRAINDICATIONS, CLINICAL PHARMACOLOGY, Drug** 484 **Interactions, and PRECAUTIONS, Drug Interactions)**

485 Concomitant use of ATRIPLA and St. John's wort (*Hypericum perforatum*) or St. John's  
486 wort-containing products is not recommended. Coadministration of NNRTIs, including  
487 efavirenz, with St. John's wort is expected to substantially decrease NNRTI  
488 concentrations and may result in suboptimal levels of efavirenz and lead to loss of  
489 virologic response and possible resistance to efavirenz or to the class of NNRTIs.

#### 490 **Psychiatric Symptoms**

491 Serious psychiatric adverse experiences have been reported in patients treated with  
492 efavirenz. In controlled trials of 1008 patients treated with regimens containing  
493 efavirenz for a mean of 2.1 years and 635 patients treated with control regimens for a  
494 mean of 1.5 years, the frequency of specific serious psychiatric events among patients  
495 who received efavirenz or control regimens, respectively, were: severe depression  
496 (2.4%, 0.9%), suicidal ideation (0.7%, 0.3%), nonfatal suicide attempts (0.5%, 0%),  
497 aggressive behavior (0.4%, 0.5%), paranoid reactions (0.4%, 0.3%), and manic  
498 reactions (0.2%, 0.3%). When psychiatric symptoms similar to those noted above were  
499 combined and evaluated as a group in a multifactorial analysis of data from Study  
500 AI266006 (006), treatment with efavirenz was associated with an increase in the  
501 occurrence of these selected psychiatric symptoms. Other factors associated with an  
502 increase in the occurrence of these psychiatric symptoms were history of injection drug  
503 use, psychiatric history, and receipt of psychiatric medication at study entry; similar  
504 associations were observed in both the efavirenz and control treatment groups. In  
505 Study 006, onset of new serious psychiatric symptoms occurred throughout the study  
506 for both efavirenz-treated and control-treated patients. One percent of efavirenz-treated  
507 patients discontinued or interrupted treatment because of one or more of these selected  
508 psychiatric symptoms. There have also been occasional postmarketing reports of death  
509 by suicide, delusions, and psychosis-like behavior, although a causal relationship to the  
510 use of efavirenz cannot be determined from these reports. Patients with serious  
511 psychiatric adverse experiences should seek immediate medical evaluation to assess  
512 the possibility that the symptoms may be related to the use of efavirenz, and if so, to  
513 determine whether the risks of continued therapy outweigh the benefits (see **ADVERSE**  
514 **REACTIONS**).

## 515 **Nervous System Symptoms**

516 Fifty-three percent of patients receiving efavirenz in controlled trials reported central  
517 nervous system symptoms compared to 25% of patients receiving control regimens.  
518 These symptoms included dizziness (28.1%), insomnia (16.3%), impaired concentration  
519 (8.3%), somnolence (7.0%), abnormal dreams (6.2%), and hallucinations (1.2%). Other  
520 reported symptoms were euphoria, confusion, agitation, amnesia, stupor, abnormal  
521 thinking, and depersonalization. The majority of these symptoms were mild-moderate  
522 (50.7%); symptoms were severe in 2.0% of patients. Overall, 2.1% of patients  
523 discontinued therapy as a result. These symptoms usually begin during the first or  
524 second day of therapy and generally resolve after the first 2–4 weeks of therapy. After  
525 4 weeks of therapy, the prevalence of nervous system symptoms of at least moderate  
526 severity ranged from 5% to 9% in patients treated with regimens containing efavirenz  
527 and from 3% to 5% in patients treated with a control regimen. Patients should be  
528 informed that these common symptoms were likely to improve with continued therapy  
529 and were not predictive of subsequent onset of the less frequent psychiatric symptoms  
530 **(see WARNINGS, Psychiatric Symptoms)**. Dosing at bedtime may improve the  
531 tolerability of these nervous system symptoms **(see ADVERSE REACTIONS and**  
532 **DOSAGE AND ADMINISTRATION)**.

533 Analysis of long-term data from Study 006, (median follow-up 180 weeks, 102 weeks,  
534 and 76 weeks for patients treated with efavirenz + zidovudine + lamivudine, efavirenz +  
535 indinavir, and indinavir + zidovudine + lamivudine, respectively) showed that, beyond 24  
536 weeks of therapy, the incidences of new-onset nervous system symptoms among  
537 efavirenz-treated patients were generally similar to those in the indinavir-containing  
538 control arm.

539 Patients receiving ATRIPLA should be alerted to the potential for additive central  
540 nervous system effects when ATRIPLA is used concomitantly with alcohol or  
541 psychoactive drugs.

542 Patients who experience central nervous system symptoms such as dizziness, impaired  
543 concentration, and/or drowsiness should avoid potentially hazardous tasks such as  
544 driving or operating machinery.

## 545 **Renal Impairment**

546 Emtricitabine and tenofovir are principally eliminated by the kidney, however efavirenz is  
547 not. Since ATRIPLA is a combination product and the dose of the individual  
548 components cannot be altered, patients with creatinine clearance <50 mL/min should  
549 not receive ATRIPLA.

550 Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal  
551 tubular injury with severe hypophosphatemia), has been reported in association with the  
552 use of tenofovir DF **(see ADVERSE REACTIONS, Post Marketing Experience)**. ~~The~~

553 It is recommended that creatinine clearance be calculated in all patients prior to  
554 initiating therapy and as clinically appropriate during therapy with ATRIPLA. Routine  
555 monitoring of calculated creatinine clearance and serum phosphorus should be  
556 performed in patients at risk for renal impairment.

557

558 ATRIPLA should be avoided with concurrent or recent use of a nephrotoxic agent.

## 559 **Reproductive Risk Potential**

560 **Pregnancy Category D:** Efavirenz may cause fetal harm when administered during  
561 the first trimester to a pregnant woman. Pregnancy should be avoided in women  
562 receiving ATRIPLA. Barrier contraception should always be used in combination with  
563 other methods of contraception (eg, oral or other hormonal contraceptives). Women of  
564 childbearing potential should undergo pregnancy testing before initiation of ATRIPLA. If  
565 this drug is used during the first trimester of pregnancy, or if the patient becomes  
566 pregnant while taking this drug, the patient should be apprised of the potential harm to  
567 the fetus.

568 There are no adequate and well-controlled studies of ATRIPLA in pregnant women.  
569 ATRIPLA should be used during pregnancy only if the potential benefit justifies the  
570 potential risk to the fetus, such as in pregnant women without other therapeutic options.

571 **Antiretroviral Pregnancy Registry:** To monitor fetal outcomes of pregnant women, an  
572 Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to  
573 register patients who become pregnant by calling (800) 258-4263.

574 **Efavirenz:** As of July 2006, the Antiretroviral Pregnancy Registry has received  
575 prospective reports of 322 pregnancies exposed to efavirenz-containing regimens,  
576 nearly all of which were first-trimester exposures (316 pregnancies). Birth defects  
577 occurred in 6 of 255 live births (first-trimester exposure) and 1 of 17 live births  
578 (second/third-trimester exposure). None of these prospectively reported defects were  
579 neural tube defects. However, there have been four retrospective reports of findings  
580 consistent with neural tube defects, including meningomyelocele. All mothers were  
581 exposed to efavirenz-containing regimens in the first trimester. Although a causal  
582 relationship of these events to the use of efavirenz has not been established, similar  
583 defects have been observed in preclinical studies of efavirenz.

584 *Animal toxicology:* Malformations have been observed in 3 of 20 fetuses/infants from  
585 efavirenz-treated cynomolgus monkeys (versus 0 of 20 concomitant controls) in a  
586 developmental toxicity study. The pregnant monkeys were dosed throughout  
587 pregnancy (postcoital days 20–150) with efavirenz 60 mg/kg daily, a dose which  
588 resulted in plasma drug concentrations similar to those in humans given 600 mg/day of  
589 efavirenz. Anencephaly and unilateral anophthalmia were observed in one fetus,  
590 microphthalmia was observed in another fetus, and cleft palate was observed in a third  
591 fetus. Efavirenz crosses the placenta in cynomolgus monkeys and produces fetal blood  
592 concentrations similar to maternal blood concentrations. Efavirenz has been shown to  
593 cross the placenta in rats and rabbits and produces fetal blood concentrations of  
594 efavirenz similar to maternal concentrations. An increase in fetal resorptions was  
595 observed in rats at efavirenz doses that produced peak plasma concentrations and AUC  
596 values in female rats equivalent to or lower than those achieved in humans given  
597 600 mg once daily of efavirenz. Efavirenz produced no reproductive toxicities when  
598 given to pregnant rabbits at doses that produced peak plasma concentrations similar to  
599 and AUC values approximately half of those achieved in humans given 600 mg once  
600 daily of efavirenz.

## 601 PRECAUTIONS

### 602 Skin Rash

603 In controlled clinical trials, 26% (266/1008) of patients treated with 600 mg efavirenz  
604 experienced new-onset skin rash compared with 17% (111/635) of patients treated in  
605 control groups. Rash associated with blistering, moist desquamation, or ulceration  
606 occurred in 0.9% (9/1008) of patients treated with efavirenz. The incidence of Grade 4  
607 rash (eg, erythema multiforme, Stevens-Johnson syndrome) in patients treated with  
608 efavirenz in all studies and expanded access was 0.1%. Rashes are usually mild-to-  
609 moderate maculopapular skin eruptions that occur within the first 2 weeks of initiating  
610 therapy with efavirenz (median time to onset of rash in adults was 11 days) and, in most  
611 patients continuing therapy with efavirenz, rash resolves within 1 month (median  
612 duration, 16 days). The discontinuation rate for rash in clinical trials was 1.7%  
613 (17/1008). ATRIPLA can be reinitiated in patients interrupting therapy because of rash.  
614 ATRIPLA should be discontinued in patients developing severe rash associated with  
615 blistering, desquamation, mucosal involvement, or fever. Appropriate antihistamines  
616 and/or corticosteroids may improve the tolerability and hasten the resolution of rash.

617 Experience with efavirenz in patients who discontinued other antiretroviral agents of the  
618 NNRTI class is limited. Nineteen patients who discontinued nevirapine because of rash  
619 have been treated with efavirenz. Nine of these patients developed mild-to-moderate  
620 rash while receiving therapy with efavirenz, and two of these patients discontinued  
621 because of rash.

### 622 Liver Enzymes

623 In patients with known or suspected history of hepatitis B or C infection and in patients  
624 treated with other medications associated with liver toxicity, monitoring of liver enzymes  
625 is recommended (**see WARNINGS, Patients Coinfected with HIV and HBV**). In  
626 patients with persistent elevations of serum transaminases to greater than five times the  
627 upper limit of the normal range, the benefit of continued therapy with ATRIPLA needs to  
628 be weighed against the unknown risks of significant liver toxicity (**see ADVERSE**  
629 **REACTIONS, Laboratory Abnormalities**).

630 Because of the extensive cytochrome P450 mediated metabolism of efavirenz and  
631 limited clinical experience in patients with hepatic impairment, caution should be  
632 exercised in administering ATRIPLA to these patients.

### 633 Bone Effects

634 In a 144-week study of treatment naïve patients, decreases in bone mineral density  
635 (BMD) were seen at the lumbar spine and hip in both arms of the study. At Week 144,  
636 there was a significantly greater mean percentage decrease from baseline in BMD at  
637 the lumbar spine in patients receiving tenofovir DF + lamivudine + efavirenz compared  
638 with patients receiving stavudine + lamivudine + efavirenz. Changes in BMD at the hip  
639 were similar between the two treatment groups. In both groups, the majority of the  
640 reduction in BMD occurred in the first 24–48 weeks of the study and this reduction was  
641 sustained through 144 weeks. Twenty-eight percent of tenofovir DF treated patients vs.  
642 21% of the comparator patients lost at least 5% of BMD at the spine or 7% of BMD at  
643 the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4  
644 patients in the tenofovir DF group and 6 patients in the comparator group. Tenofovir DF

645 was associated with significant increases in biochemical markers of bone metabolism  
646 (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide,  
647 and urinary N-telopeptide), suggesting increased bone turnover. Serum parathyroid  
648 hormone levels and 1,25 Vitamin D levels were also higher in patients receiving  
649 tenofovir DF. The effects of tenofovir DF associated changes in BMD and biochemical  
650 markers on long-term bone health and future fracture risk are unknown. For additional  
651 information, please consult the tenofovir DF prescribing information.

652 Cases of osteomalacia (associated with proximal renal tubulopathy) have been reported  
653 in association with the use of tenofovir DF (**see Adverse Reactions, Post Marketing**  
654 **Experience**).

655

656 Bone monitoring should be considered for HIV infected patients who have a history of  
657 pathologic bone fracture or are at risk for osteopenia. Although the effect of  
658 supplementation with calcium and vitamin D was not studied, such supplementation  
659 may be beneficial for all patients. If bone abnormalities are suspected then appropriate  
660 consultation should be obtained.

### 661 **Convulsions**

662 Convulsions have been observed in patients receiving efavirenz, generally in the  
663 presence of known medical history of seizures. Caution must be taken in any patient  
664 with a history of seizures.

665 Patients who are receiving concomitant anticonvulsant medications primarily  
666 metabolized by the liver, such as phenytoin and phenobarbital, may require periodic  
667 monitoring of plasma levels (**see PRECAUTIONS, Drug Interactions**).

668 *Animal toxicology:* Nonsustained convulsions were observed in 6 of 20 monkeys  
669 receiving efavirenz at doses yielding plasma AUC values 4- to 13-fold greater than  
670 those in humans given the recommended dose.

### 671 **Fat Redistribution**

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

### 677 **Immune Reconstitution Syndrome**

678 Immune reconstitution syndrome has been reported in patients treated with combination  
679 antiretroviral therapy, including the components of ATRIPLA. During the initial phase of  
680 combination antiretroviral treatment, patients whose immune system responds may  
681 develop an inflammatory response to indolent or residual opportunistic infections (such  
682 as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jiroveci* pneumonia  
683 (PCP), or tuberculosis), which may necessitate further evaluation and treatment.

684 **Information for Patients**

685 A statement to patients and healthcare providers is included on the product's bottle  
686 labels: **ALERT: Find out about medicines that should NOT be taken with**  
687 **ATRIPLA.** A Patient Package Insert (PPI) for ATRIPLA is available for patient  
688 information.

689 ATRIPLA is not a cure for HIV infection and patients may continue to experience  
690 illnesses associated with HIV infection, including opportunistic infections. Patients  
691 should remain under the care of a physician when using ATRIPLA.

692 Patients should be advised that:

- 693 • the use of ATRIPLA has not been shown to reduce the risk of transmission of HIV to  
694 others through sexual contact or blood contamination,
- 695 • the long term effects of ATRIPLA are unknown,
- 696 • ATRIPLA Tablets are for oral ingestion only,
- 697 • it is important to take ATRIPLA on a regular dosing schedule to avoid missing doses,
- 698 • redistribution or accumulation of body fat may occur in patients receiving  
699 antiretroviral therapy and that the cause and long-term health effects of these  
700 conditions are not known.
- 701 • ATRIPLA should not be coadministered with SUSTIVA, EMTRIVA, VIREAD, or  
702 TRUVADA, or drugs containing lamivudine, including Combivir, Epivir, Epivir-HBV,  
703 Epzicom, or Trizivir.

704 Patients should be advised to take ATRIPLA on an empty stomach.

705 Patients should be informed that central nervous system symptoms including dizziness,  
706 insomnia, impaired concentration, drowsiness, and abnormal dreams are commonly  
707 reported during the first weeks of therapy with efavirenz. Dosing at bedtime may  
708 improve the tolerability of these symptoms, and these symptoms are likely to improve  
709 with continued therapy. Patients should be alerted to the potential for additive central  
710 nervous system effects when ATRIPLA is used concomitantly with alcohol or  
711 psychoactive drugs. Patients should be instructed that if they experience these  
712 symptoms they should avoid potentially hazardous tasks such as driving or operating  
713 machinery (**see WARNINGS, Nervous System Symptoms, ADVERSE REACTIONS,**  
714 **and DOSAGE AND ADMINISTRATION**). In clinical trials, patients who develop central  
715 nervous system symptoms were not more likely to subsequently develop psychiatric  
716 symptoms (**see WARNINGS, Psychiatric Symptoms**).

717 Patients should also be informed that serious psychiatric symptoms including severe  
718 depression, suicide attempts, aggressive behavior, delusions, paranoia, and psychosis-  
719 like symptoms have also been reported in patients receiving efavirenz. Patients should  
720 be informed that if they experience severe psychiatric adverse experiences they should  
721 seek immediate medical evaluation to assess the possibility that the symptoms may be  
722 related to the use of ATRIPLA, and if so, to determine whether discontinuation of  
723 ATRIPLA may be required. Patients should also inform their physician of any history of  
724 mental illness or substance abuse (**see WARNINGS, Psychiatric Symptoms**).

725 Patients should be informed that another common side effect is rash. These rashes  
726 usually go away without any change in treatment. In a small number of patients, rash  
727 may be serious. Patients should be advised that they should contact their physician  
728 promptly if they develop a rash.

729 Women receiving ATRIPLA should be instructed to avoid pregnancy (**see WARNINGS,**  
730 **Reproductive Risk Potential**). A reliable form of barrier contraception should always  
731 be used in combination with other methods of contraception, including oral or other  
732 hormonal contraception, because the effects of efavirenz on hormonal contraceptives  
733 are not fully characterized. Women should be advised to notify their physician if they  
734 become pregnant or plan to become pregnant while taking ATRIPLA. If this drug is  
735 used during the first trimester of pregnancy, or if the patient becomes pregnant while  
736 taking this drug, she should be apprised of the potential harm to the fetus.

737 ATRIPLA may interact with some drugs; therefore, patients should be advised to report  
738 to their doctor the use of any other prescription, nonprescription medication, or herbal  
739 products, particularly St. John's wort.

#### 740 **Animal Toxicology**

741 Tenofovir and tenofovir DF administered in toxicology studies to rats, dogs and  
742 monkeys at exposures (based on AUCs) greater than or equal to 6-fold those observed  
743 in humans caused bone toxicity. In monkeys the bone toxicity was diagnosed as  
744 osteomalacia. Osteomalacia observed in monkeys appeared to be reversible upon  
745 dose reduction or discontinuation of tenofovir. In rats and dogs, the bone toxicity  
746 manifested as reduced bone mineral density. The mechanism(s) underlying bone  
747 toxicity is unknown.

748 Evidence of renal toxicity was noted in 4 animal species administered tenofovir and  
749 tenofovir DF. Increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia  
750 and/or calciuria and decreases in serum phosphate were observed to varying degrees  
751 in these animals. These toxicities were noted at exposures (based on AUCs) 2–20  
752 times higher than those observed in humans. The relationship of the renal  
753 abnormalities, particularly the phosphaturia, to the bone toxicity is not known.

#### 754 **Drug Interactions (see CONTRAINDICATIONS and CLINICAL PHARMACOLOGY,** 755 **Drug Interactions)**

756 **Efavirenz:** Efavirenz has been shown in vivo to induce CYP3A4. Other compounds  
757 that are substrates of CYP3A4 may have decreased plasma concentrations when  
758 coadministered with efavirenz. In vitro studies have demonstrated that efavirenz inhibits  
759 2C9, 2C19, and 3A4 isozymes in the range of observed efavirenz plasma  
760 concentrations. Coadministration of efavirenz with drugs primarily metabolized by these  
761 isozymes may result in altered plasma concentrations of the coadministered drug.  
762 Therefore, appropriate dose adjustments may be necessary for these drugs.

763 Drugs which induce CYP3A4 activity (eg, phenobarbital, rifampin, rifabutin) would be  
764 expected to increase the clearance of efavirenz resulting in lowered plasma  
765 concentrations.

766 **Emtricitabine and tenofovir disoproxil fumarate:** Since emtricitabine and tenofovir  
767 are primarily eliminated by the kidneys, coadministration of ATRIPLA with drugs that

768 reduce renal function or compete for active tubular secretion may increase serum  
769 concentrations of emtricitabine, tenofovir, and/or other renally eliminated drugs. Some  
770 examples include, but are not limited to, acyclovir, adefovir dipivoxil, cidofovir,  
771 ganciclovir, valacyclovir, and valganciclovir.

772 Coadministration of tenofovir DF and didanosine (Videx, Videx EC) should be  
773 undertaken with caution and patients receiving this combination should be monitored  
774 closely for didanosine-associated adverse events. Didanosine should be discontinued  
775 in patients who develop didanosine-associated adverse events (for didanosine dosing  
776 adjustment recommendations, **see Table 8 in the PRECAUTIONS Section**).

777 Suppression of CD4 cell counts has been observed in patients receiving tenofovir DF  
778 with didanosine at a dose of 400 mg daily.

779 Atazanavir and lopinavir/ritonavir have been shown to increase tenofovir concentrations.  
780 The mechanism of this interaction is unknown. Higher tenofovir concentrations could  
781 potentiate tenofovir-associated adverse events, including renal disorders. Patients  
782 receiving either atazanavir or lopinavir/ritonavir with tenofovir DF should be monitored  
783 for tenofovir-associated adverse events. ATRIPLA should be discontinued in patients  
784 who develop tenofovir-associated adverse events (for atazanavir dosing adjustment  
785 recommendations, **(see Table 8 in the PRECAUTIONS Section)**).

786 Other important drug interaction information for ATRIPLA is summarized in Table 7 and  
787 8. The drug interactions described are based on studies conducted with efavirenz,  
788 emtricitabine or tenofovir DF as individual agents or are potential drug interactions; no  
789 drug interaction studies have been conducted using ATRIPLA. The tables include  
790 potentially significant interactions, but are not all inclusive.

791 **Table 7 Drugs That Are Contraindicated or Not Recommended for Use With ATRIPLA**

Drug Class: Drug Name	Clinical Comment
Antifungal: voriconazole	CONTRAINDICATED because efavirenz significantly decreases voriconazole plasma concentrations, and coadministration may decrease the therapeutic effectiveness of voriconazole. Also, voriconazole significantly increases efavirenz plasma concentrations, which may increase the risk of efavirenz-associated side effects. See Tables 1 and 2.
Antihistamine: astemizole	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antimigraine: ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine)	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
Antiretrovirals: EMTRIVA, VIREAD, TRUVADA, SUSTIVA, Combivir, Epivir, Epivir-HBV, Epzicom, or Trizivir.	Not for use with ATRIPLA because the active ingredients of EMTRIVA (emtricitabine), VIREAD (tenofovir DF), TRUVADA (emtricitabine/tenofovir DF) and SUSTIVA (efavirenz) are components of ATRIPLA. Lamivudine, which is similar to emtricitabine, is a component of Combivir, Epivir, Epivir-HBV, Epzicom, and Trizivir.
Benzodiazepines: midazolam, triazolam	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.
Calcium channel blocker: bepridil	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
GI motility agent: cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Neuroleptic: pimozide	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
St. John's wort ( <i>Hypericum perforatum</i> )	NOT RECOMMENDED: Expected to substantially decrease plasma levels of efavirenz; has not been studied in combination with efavirenz.

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793  
794

**Table 8 Established<sup>1</sup> and Other Potentially Significant<sup>2</sup> Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction**

Concomitant Drug Class: Drug Name	Effect	Clinical Comment
<i>Antiretroviral agents</i>		
Protease inhibitor: Amprenavir	↓ amprenavir concentration	Efavirenz has the potential to decrease serum concentrations of amprenavir.
Protease inhibitor: Fosamprenavir calcium	↓ amprenavir concentration	Fosamprenavir (unboosted): Appropriate doses of fosamprenavir and ATRIPLA with respect to safety and efficacy have not been established. Fosamprenavir/ritonavir: An additional 100 mg/day (300 mg total) of ritonavir is recommended when ATRIPLA is administered with fosamprenavir/ritonavir once daily. No change in the ritonavir dose is required when ATRIPLA is administered with fosamprenavir plus ritonavir twice daily.
Protease inhibitor: Atazanavir	↓ atazanavir concentration ↑ tenofovir concentration	Plasma concentrations of atazanavir were decreased by both efavirenz and tenofovir DF. Sufficient data are not available to make a dosing recommendation for atazanavir or atazanavir/ritonavir with ATRIPLA. Therefore, co-administration of ATRIPLA and atazanavir is not recommended due to concerns regarding decreased atazanavir concentrations.
Protease inhibitor: Indinavir	↓ indinavir concentration	The optimal dose of indinavir, when given in combination with efavirenz, is not known. Increasing the indinavir dose to 1000 mg every 8 hours does not compensate for the increased indinavir metabolism due to efavirenz.
Protease inhibitor: Lopinavir/ritonavir	↓ lopinavir concentration ↑ tenofovir concentration	A dose increase of lopinavir/ritonavir to 600/150 mg (3 tablets) twice daily may be considered when used in combination with efavirenz in treatment-experienced patients where decreased susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). <b>Patients should be monitored for tenofovir-associated adverse events. ATRIPLA should be discontinued in patients who develop tenofovir-associated adverse events.</b>
Protease inhibitor: Ritonavir	↑ ritonavir concentration ↑ efavirenz concentration	When ritonavir 500 mg every 12 hours was coadministered with efavirenz 600 mg once daily, the combination was associated with a higher frequency of adverse clinical experiences (eg, dizziness, nausea, paresthesia) and laboratory abnormalities (elevated liver enzymes). Monitoring of liver enzymes is recommended when ATRIPLA is used in combination with ritonavir.
Protease inhibitor: Saquinavir	↓ saquinavir concentration	Should not be used as sole protease inhibitor in combination with ATRIPLA.

Concomitant Drug Class: Drug Name	Effect	Clinical Comment
NRTI: Didanosine	↑ didanosine concentration	Higher didanosine concentrations could potentiate didanosine-associated adverse events, including pancreatitis, and neuropathy. <b>In adults weighing &gt;60 kg, the didanosine dose should be reduced to 250 mg if coadministered with ATRIPLA. Data are not available to recommend a dose adjustment of didanosine for patients weighing &lt;60 kg.</b> When coadministered, ATRIPLA and Videx EC may be taken under fasted conditions or with a light meal (<400 kcal, 20% fat). Coadministration of didanosine buffered formulation with ATRIPLA should be under fasted conditions. <b>Coadministration of ATRIPLA and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse events. For additional information, please consult the Videx / Videx EC (didanosine) prescribing information.</b>
<i>Other agents</i>		
Anticoagulant: Warfarin	↑ or ↓ warfarin concentration	Plasma concentrations and effects potentially increased or decreased by efavirenz.
Anticonvulsants: Carbamazepine  Phenytoin Phenobarbital	↓ carbamazepine concentration ↓ efavirenz concentration  ↓ anticonvulsant concentration ↓ efavirenz concentration	There are insufficient data to make a dose recommendation for ATRIPLA. Alternative anticonvulsant treatment should be used.  Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.
Antidepressant: Sertraline	↓ sertraline concentration	Increases in sertraline dose should be guided by clinical response.

<b>Concomitant Drug Class: Drug Name</b>	<b>Effect</b>	<b>Clinical Comment</b>
<p>Antifungals:</p> <p>Itraconazole</p> <p>Ketoconazole</p>	<p>↓ itraconazole<sup>1</sup> concentration</p> <p>↓ hydroxy-itraconazole<sup>1</sup> concentration</p> <p>↓ ketoconazole concentration</p>	<p>Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered.</p> <p>Drug interaction studies with ATRIPLA and ketoconazole have not been conducted. Efavirenz has the potential to decrease plasma concentrations of ketoconazole.</p>
<p>Anti-infective:</p> <p>Clarithromycin</p>	<p>↓ clarithromycin concentration</p> <p>↑ 14-OH metabolite concentration</p>	<p>Clinical significance unknown. In uninfected volunteers, 46% developed rash while receiving efavirenz and clarithromycin. No dose adjustment of ATRIPLA is recommended when given with clarithromycin. Alternatives to clarithromycin, such as azithromycin, should be considered. Other macrolide antibiotics, such as erythromycin, have not been studied in combination with ATRIPLA.</p>
<p>Antimycobacterial:</p> <p>Rifabutin</p>	<p>↓ rifabutin concentration</p>	<p>Increase daily dose of rifabutin by 50%. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week.</p>
<p>Antimycobacterial:</p> <p>Rifampin</p>	<p>↓ efavirenz<sup>1</sup> concentration</p>	<p>Clinical significance of reduced efavirenz concentration is unknown. Dosing recommendations for concomitant use of ATRIPLA and rifampin have not been established.</p>
<p>Calcium channel blockers:</p> <p>Diltiazem</p> <p>Others (eg, felodipine, nicardipine, nifedipine, verapamil)</p>	<p>↓ diltiazem<sup>1</sup> concentration</p> <p>↓ desacetyl diltiazem<sup>1</sup> concentration</p> <p>↓ N-monodesmethyl diltiazem<sup>1</sup> concentration</p> <p>↓ calcium channel blocker</p>	<p>Diltiazem dose adjustments should be guided by clinical response (refer to the complete prescribing information for diltiazem). No dose adjustment of ATRIPLA is necessary when administered with diltiazem.</p> <p>No data are available on the potential interactions of efavirenz with other calcium channel blockers that are substrates of the CYP3A4 enzyme. The potential exists for reduction in plasma concentrations of the calcium channel blocker. Dose adjustments should be guided by clinical response (refer to the complete prescribing information for the calcium channel blocker).</p>
<p>HMG-CoA reductase inhibitors:</p> <p>Atorvastatin</p> <p>Pravastatin</p> <p>Simvastatin</p>	<p>↓ atorvastatin<sup>1</sup> concentration</p> <p>↓ pravastatin<sup>1</sup> concentration</p> <p>↓ simvastatin<sup>1</sup> concentration</p>	<p>Plasma concentrations of atorvastatin, pravastatin, and simvastatin decreased with efavirenz. Consult the complete prescribing information for the HMG-CoA reductase inhibitor for guidance on individualizing the dose.</p>

Concomitant Drug Class: Drug Name	Effect	Clinical Comment
Narcotic analgesic: Methadone	↓ methadone concentration	Coadministration of efavirenz in HIV-infected individuals with a history of injection drug use resulted in decreased plasma levels of methadone and signs of opiate withdrawal. Methadone dose was increased by a mean of 22% to alleviate withdrawal symptoms. Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.
Oral contraceptive: Ethinyl estradiol	↑ ethinyl estradiol concentration	Clinical significance unknown. Because the potential interaction of efavirenz with oral contraceptives has not been fully characterized, a reliable method of barrier contraception should be used in addition to oral contraceptives.

- 795 1. See Tables 1–5  
796 2. This table is not all inclusive.

## 797 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

798 **Efavirenz:** Long-term carcinogenicity studies in mice and rats were carried out with  
799 efavirenz. Mice were dosed with 0, 25, 75, 150, or 300 mg/kg/day for 2 years.  
800 Incidences of hepatocellular adenomas and carcinomas and pulmonary  
801 alveolar/bronchiolar adenomas were increased above background in females. No  
802 increases in tumor incidence above background were seen in males. In studies in  
803 which rats were administered efavirenz at doses of 0, 25, 50, or 100 mg/kg/day for 2  
804 years, no increases in tumor incidence above background were observed. The  
805 systemic exposure (based on AUCs) in mice was approximately 1.7-fold that in humans  
806 receiving the 600-mg/day dose. The exposure in rats was lower than that in humans.  
807 The mechanism of the carcinogenic potential is unknown. However, in genetic  
808 toxicology assays, efavirenz showed no evidence of mutagenic or clastogenic activity in  
809 a battery of in vitro and in vivo studies. These included bacterial mutation assays in  
810 *S. typhimurium* and *E. coli*, mammalian mutation assays in Chinese hamster ovary  
811 cells, chromosome aberration assays in human peripheral blood lymphocytes or  
812 Chinese hamster ovary cells, and an in vivo mouse bone marrow micronucleus assay.  
813 Given the lack of genotoxic activity of efavirenz, the relevance to humans of neoplasms  
814 in efavirenz-treated mice is not known.

815 Efavirenz did not impair mating or fertility of male or female rats, and did not affect  
816 sperm of treated male rats. The reproductive performance of offspring born to female  
817 rats given efavirenz was not affected. As a result of the rapid clearance of efavirenz in  
818 rats, systemic drug exposures achieved in these studies were equivalent to or below  
819 those achieved in humans given therapeutic doses of efavirenz.

820 **Emtricitabine:** In long-term carcinogenicity studies of emtricitabine, no drug-related  
821 increases in tumor incidence were found in mice at doses up to 750 mg/kg/day (26  
822 times the human systemic exposure at the therapeutic dose of 200 mg/day) or in rats at  
823 doses up to 600 mg/day (31 times the human systemic exposure at the therapeutic  
824 dose).

825 Emtricitabine was not genotoxic in the reverse mutation bacterial test (Ames test),  
826 mouse lymphoma or mouse micronucleus assays.

827 Emtricitabine did not affect fertility in male rats at approximately 140-fold or in male and  
828 female mice at approximately 60-fold higher exposures (AUC) than in humans given the  
829 recommended 200 mg daily dose. Fertility was normal in the offspring of mice exposed  
830 daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of  
831 approximately 60-fold higher than human exposures at the recommended 200 mg daily  
832 dose.

833 **Tenofovir disoproxil fumarate:** Long-term oral carcinogenicity studies of tenofovir DF  
834 in mice and rats were carried out at exposures up to approximately 16 times (mice) and  
835 5 times (rats) those observed in humans at the therapeutic dose for HIV infection. At  
836 the high dose in female mice, liver adenomas were increased at exposures 16 times  
837 that in humans. In rats, the study was negative for carcinogenic findings at exposures  
838 up to 5 times that observed in humans at the therapeutic dose.

839 Tenofovir DF was mutagenic in the in vitro mouse lymphoma assay and negative in an  
840 in vitro bacterial mutagenicity test (Ames test). In an in vivo mouse micronucleus assay,  
841 tenofovir DF was negative when administered to male mice.

842 There were no effects on fertility, mating performance or early embryonic development  
843 when tenofovir DF was administered to male rats at a dose equivalent to 10 times the  
844 human dose based on body surface area comparisons for 28 days prior to mating and  
845 to female rats for 15 days prior to mating through day seven of gestation. There was,  
846 however, an alteration of the estrous cycle in female rats.

#### 847 **Pregnancy**

848 **Pregnancy Category D (see WARNINGS, Reproductive Risk Potential)**

#### 849 **Nursing Mothers**

850 **The Centers for Disease Control and Prevention recommend that HIV-infected**  
851 **mothers not breast-feed their infants to avoid risking postnatal transmission of**  
852 **HIV.** Studies in rats have demonstrated that both efavirenz and tenofovir are secreted  
853 in milk. It is not known whether efavirenz, emtricitabine, or tenofovir is excreted in  
854 human milk. Because of both the potential for HIV transmission and the potential for  
855 serious adverse reactions in nursing infants, **mothers should be instructed not to**  
856 **breast-feed if they are receiving ATRIPLA.**

#### 857 **Pediatric Use**

858 ATRIPLA is not recommended for patients less than 18 years of age because it is a  
859 fixed-dose combination tablet containing a component, tenofovir DF, for which safety  
860 and efficacy have not been established in this age group.

#### 861 **Geriatric Use**

862 Clinical studies of efavirenz, emtricitabine, or tenofovir DF did not include sufficient  
863 numbers of subjects aged 65 and over to determine whether they respond differently  
864 from younger subjects. In general, dose selection for the elderly patients should be  
865 cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac  
866 function, and of concomitant disease or other drug therapy.

867 **ADVERSE REACTIONS**

868 For additional safety information about SUSTIVA (efavirenz), EMTRIVA (emtricitabine)  
869 or VIREAD (tenofovir DF) in combination with other antiretroviral agents, consult the  
870 Prescribing Information for these products.

871 In addition to the adverse events in study 934 (Table 9), the following adverse events  
872 were observed in clinical studies of efavirenz, emtricitabine, or tenofovir DF in  
873 combination with other antiretroviral agents.

874 **Efavirenz:** The most significant adverse events observed in patients treated with  
875 efavirenz are nervous system symptoms (**see WARNINGS, Nervous System**  
876 **Symptoms**), psychiatric symptoms (**see WARNINGS, Psychiatric Symptoms**), and  
877 rash (**see PRECAUTIONS, Skin Rash**).

878 Selected clinical adverse experiences of moderate or severe intensity observed in  $\geq 2\%$   
879 of efavirenz-treated patients in two controlled clinical trials included pain, impaired  
880 concentration, anorexia, dyspepsia, abdominal pain, anxiety, nervousness, and pruritus.

881 Pancreatitis has been reported, although a causal relationship with efavirenz has not  
882 been established. Asymptomatic increases in serum amylase levels were observed in a  
883 significantly higher number of patients treated with efavirenz 600 mg than in control  
884 patients.

885 **Emtricitabine and tenofovir disoproxil fumarate:** Adverse events that occurred in at  
886 least 5% of patients receiving emtricitabine or tenofovir DF with other antiretroviral  
887 agents in clinical trials include anxiety, arthralgia, increased cough, dyspepsia, fever,  
888 myalgia, pain, abdominal pain, back pain, paresthesia, peripheral neuropathy (including  
889 peripheral neuritis and neuropathy), pneumonia, rhinitis and rash event (including rash,  
890 pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash and allergic  
891 reaction).

892 Skin discoloration has been reported with higher frequency among emtricitabine treated  
893 patients. Skin discoloration, manifested by hyperpigmentation on the palms and/or  
894 soles was generally mild and asymptomatic. The mechanism and clinical significance  
895 are unknown.

896 In addition to the laboratory abnormalities described for Study 934 (Table 10),  
897 Grade 3/4 elevations of bilirubin ( $>2.5 \times \text{ULN}$ ), pancreatic amylase ( $>2.0 \times \text{ULN}$ ), serum  
898 glucose ( $<40$  or  $>250$  mg/dL), serum lipase ( $>2.0 \times \text{ULN}$ ), and urine glucose ( $\geq 3+$ )  
899 occurred in up to 3% of patients treated with emtricitabine or tenofovir DF with other  
900 antiretroviral agents in clinical trials.

901 **Clinical Trials**

902 **Study 934 - Treatment Emergent Adverse Events:** Study 934 was an open-label  
903 active-controlled study in which 511 antiretroviral-naïve patients received either  
904 emtricitabine + tenofovir DF administered in combination with efavirenz (N=257) or  
905 zidovudine/lamivudine administered in combination with efavirenz (N=254). Adverse  
906 events observed in this study, regardless of treatment relationship, are shown in Table  
907 9.

908 **Table 9 Selected Treatment-Emergent Adverse Events (Grades 2–4) Reported in ≥3%**  
 909 **in Any Treatment Group in Study 934 (0–48 weeks)**

	FTC + TDF + EFV	AZT/3TC + EFV
	(N=257)	(N=254)
Gastrointestinal Disorder		
Diarrhea	7%	4%
Nausea	8%	6%
Vomiting	1%	4%
General Disorders and Administration Site Condition		
Fatigue	7%	6%
Infections and Infestations		
Sinusitis	4%	2%
Upper respiratory tract infections	3%	3%
Nasopharyngitis	3%	1%
Nervous System Disorders		
Somnolence	3%	2%
Headache	5%	4%
Dizziness	8%	7%
Psychiatric Disorders		
Depression	4%	7%
Insomnia	4%	5%
Abnormal dreams	4%	3%
Skin and Subcutaneous Tissue Disorders		
Rash	5%	4%

910

911 **Laboratory Abnormalities:** Laboratory abnormalities observed in this study were  
 912 generally consistent with those seen in other studies (Table 10).

913 **Table 10 Significant Laboratory Abnormalities Reported in ≥1% in Any Treatment**  
 914 **Group in Study 934 (0–48 weeks)**

	FTC + TDF + EFV	AZT/3TC + EFV
	(N=257)	(N=254)
Any ≥ Grade 3 Laboratory Abnormality	25%	22%
Fasting Cholesterol (>240 mg/dL)	15%	17%
Creatine Kinase (M: >990 U/L) (F: >845 U/L)	7%	6%
Serum Amylase (>175 U/L)	7%	3%
Alkaline Phosphatase (>550 U/L)	1%	0%
AST (M: >180 U/L) (F: >170 U/L)	3%	2%
ALT (M: >215 U/L) (F: >170 U/L)	2%	2%
Hemoglobin (<8.0 mg/dL)	0%	3%
Hyperglycemia (>250 mg/dL)	1%	1%
Hematuria (>75 RBC/HPF)	2%	2%
Neutrophils (<750/mm <sup>3</sup> )	3%	4%
Fasting Triglycerides (>750 mg/dL)	4%	2%

915  
 916 **Lipids:** In Study 934 at Week 48, the mean increase from baseline fasting triglyceride  
 917 concentrations was 3 mg/dL for the tenofovir DF, emtricitabine and efavirenz group and  
 918 31 mg/dL for the zidovudine/lamivudine and efavirenz group. For fasting total, LDL, and  
 919 HDL cholesterol concentrations, the mean increases from baseline were 21 mg/dL, 13  
 920 mg/dL, and 6 mg/dL, respectively, for the tenofovir DF group and 35 mg/dL, 20 mg/dL,  
 921 and 9 mg/dL, respectively, for the zidovudine/lamivudine group.

922  
 923 **Hepatic Events:** In Study 934, 10 patients treated with efavirenz, emtricitabine, and  
 924 tenofovir DF and 16 patients treated with efavirenz and fixed-dose  
 925 zidovudine/lamivudine were hepatitis C antibody positive. Among these HCV coinfecting  
 926 patients, one patient (1/10) in the efavirenz, emtricitabine and tenofovir DF arm had  
 927 elevations in ALT and AST to greater than five times ULN through 48 weeks. One  
 928 patient (1/16) in the fixed-dose zidovudine/lamivudine arm had elevations in ALT to  
 929 greater than five times ULN through 48 weeks. Nine patients treated with efavirenz,  
 930 emtricitabine and tenofovir DF and 4 patients treated with efavirenz and fixed-dose  
 931 zidovudine/lamivudine were hepatitis B surface antigen positive. None of these patients  
 932 had treatment-emergent elevations in ALT and AST to greater than five times ULN  
 933 through 48 weeks. No HBV and/or HCV coinfecting patient discontinued from the study  
 934 due to hepatobiliary disorders (**see PRECAUTIONS, Liver Enzymes**).

935 **Post Marketing Experience**

936 The following events have been identified during post-approval use of efavirenz,  
937 emtricitabine, or tenofovir DF. Because they are reported voluntarily from a population  
938 of unknown size, estimates of frequency cannot be made. These events have been  
939 chosen for inclusion because of a combination of their seriousness, frequency of  
940 reporting or potential causal connection.

941 **Efavirenz:**

942 **CARDIAC DISORDERS**

943 Palpitations

944 **EAR AND LABYRINTH DISORDERS**

945 Tinnitus

946 **ENDOCRINE DISORDERS**

947 Gynecomastia

948 **EYE DISORDERS**

949 Abnormal vision

950 **GASTROINTESTINAL DISORDERS**

951 Constipation, Malabsorption

952 **GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS**

953 Asthenia

954 **HEPATOBIILIARY DISORDERS**

955 Hepatic enzyme increase, Hepatic failure, Hepatitis

956 **IMMUNE SYSTEM DISORDERS**

957 Allergic reactions

958 **METABOLISM AND NUTRITION DISORDERS**

959 Redistribution/accumulation of body fat (**see PRECAUTIONS, Fat Redistribution**),

960 Hypercholesterolemia, Hypertriglyceridemia

961 **MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS**

962 Arthralgia, Myalgia, Myopathy

963 **NERVOUS SYSTEM DISORDERS**

964 Abnormal coordination, Ataxia, Convulsions, Hypoesthesia, Paresthesia, Neuropathy,

965 Tremor

966 **PSYCHIATRIC DISORDERS**

967 Aggressive reactions, Agitation, Delusions, Emotional lability, Mania, Neurosis,

968 Paranoia, Psychosis, Suicide

969 **RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS**

970 Dyspnea

971 **SKIN AND SUBCUTANEOUS TISSUE DISORDERS**

972 Flushing, Erythema multiforme, Nail disorders, Photoallergic dermatitis, Skin

973 discoloration, Stevens-Johnson syndrome

974 **Emtricitabine:** No additional events have been identified for inclusion in this section.

975 **Tenofovir disoproxil fumarate:**

976 IMMUNE SYSTEM DISORDERS

977 Allergic reaction

978 METABOLISM AND NUTRITION DISORDERS

979 Hypophosphatemia, Lactic acidosis

980 RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS

981 Dyspnea

982 GASTROINTESTINAL DISORDERS

983 Abdominal pain, Increased amylase, Pancreatitis

984 HEPATOBILIARY DISORDERS

985 Increased liver enzymes, Hepatitis

986 SKIN AND SUBCUTANEOUS TISSUE DISORDERS

987 Rash

988 MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS

989 Myopathy, Osteomalacia (both associated with proximal renal tubulopathy)

990 RENAL AND URINARY DISORDERS

991 Renal insufficiency, Renal failure, Acute renal failure, Fanconi syndrome, Proximal tubulopathy, Proteinuria, Increased creatinine, Acute tubular necrosis, Nephrogenic diabetes insipidus, Polyuria, Interstitial nephritis (including acute cases).

992

993

994 GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS

995 Asthenia

996 **OVERDOSAGE**

997 If overdose occurs, the patient should be monitored for evidence of toxicity, including

998 monitoring of vital signs and observation of the patient's clinical status; standard

999 supportive treatment should then be applied as necessary. Administration of activated

1000 charcoal may be used to aid removal of unabsorbed efavirenz. Hemodialysis can

1001 remove both emtricitabine and tenofovir DF (refer to detailed information below), but is

1002 unlikely to significantly remove efavirenz from the blood.

1003 **Efavirenz:** Some patients accidentally taking 600 mg twice daily have reported

1004 increased nervous system symptoms. One patient experienced involuntary muscle

1005 contractions.

1006 **Emtricitabine:** Limited clinical experience is available at doses higher than the

1007 therapeutic dose of emtricitabine. In one clinical pharmacology study single doses of

1008 emtricitabine 1200 mg were administered to 11 patients. No severe adverse reactions

1009 were reported.

1010 Hemodialysis treatment removes approximately 30% of the emtricitabine dose over a

1011 3-hour dialysis period starting within 1.5 hours of emtricitabine dosing (blood flow rate of

1012 400 mL/min and a dialysate flow rate of 600 mL/min). It is not known whether

1013 emtricitabine can be removed by peritoneal dialysis.

1014 **Tenofovir disoproxil fumarate:** Limited clinical experience at doses higher than the  
1015 therapeutic dose of tenofovir DF 300 mg is available. In one study, 600 mg tenofovir DF  
1016 was administered to 8 patients orally for 28 days, and no severe adverse reactions were  
1017 reported. The effects of higher doses are not known.

1018 Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of  
1019 approximately 54%. Following a single 300 mg dose of tenofovir DF, a 4-hour  
1020 hemodialysis session removed approximately 10% of the administered tenofovir dose.

## 1021 **DOSAGE AND ADMINISTRATION**

1022 **Adults:** The dose of ATRIPLA is one tablet once daily taken orally on an empty  
1023 stomach. Dosing at bedtime may improve the tolerability of nervous system symptoms.

1024 **Pediatrics:** ATRIPLA is not recommended for use in patients <18 years of age.

1025 **Renal Impairment:** Because ATRIPLA is a fixed-dose combination, it should not be  
1026 prescribed for patients requiring dosage adjustment such as those with moderate or  
1027 severe renal impairment (creatinine clearance <50 mL/min).

## 1028 **HOW SUPPLIED**

1029 ATRIPLA is available as tablets. Each tablet contains 600 mg of efavirenz, 200 mg of  
1030 emtricitabine and 300 mg of tenofovir DF (which is equivalent to 245 mg of tenofovir  
1031 disoproxil). The tablets are pink, capsule-shaped, film-coated, debossed with “123” on  
1032 one side and plain-faced on the other side. Each bottle contains 30 tablets (NDC  
1033 15584-0101-1) and silica gel desiccant, and is closed with a child-resistant closure.

1034 Store at 25 °C (77 °F); excursions permitted to 15–30 °C (59–86 °F) [see USP  
1035 Controlled Room Temperature].

- 1036 • Keep container tightly closed.
- 1037 • Dispense only in original container.
- 1038 • Do not use if seal over bottle opening is broken or missing.

1039 Bristol-Myers Squibb & Gilead Sciences, LLC

1040 Foster City, CA 94404

1041 February 2008

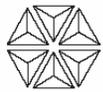
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**GILEAD**

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**Patient Information**  
**ATRIPLA™ (uh TRIP luh) Tablets**

1054 **ALERT: Find out about medicines that should NOT be taken with ATRIPLA.**

1055 Please also read the section "**MEDICINES YOU SHOULD NOT TAKE WITH**  
1056 **ATRIPLA.**"

1057 Generic name: efavirenz, emtricitabine and tenofovir disoproxil fumarate  
1058 (eh FAH vih renz, em tri SIT uh bean and te NOE' fo veer dye soe PROX il  
1059 FYOU mar ate)

1060 Read the Patient Information that comes with ATRIPLA before you start taking it  
1061 and each time you get a refill since there may be new information. This  
1062 information does not take the place of talking to your healthcare provider about  
1063 your medical condition or treatment. You should stay under a healthcare  
1064 provider's care when taking ATRIPLA. **Do not change or stop your medicine**  
1065 **without first talking with your healthcare provider.** Talk to your healthcare  
1066 provider or pharmacist if you have any questions about ATRIPLA.

1067 **What is the most important information I should know about ATRIPLA?**

1068 • **Some people who have taken medicine like ATRIPLA (which contains**  
1069 **nucleoside analogs) have developed a serious condition called lactic**  
1070 **acidosis** (build up of an acid in the blood). Lactic acidosis can be a medical  
1071 emergency and may need to be treated in the hospital. **Call your healthcare**  
1072 **provider right away if you get the following signs or symptoms of lactic**  
1073 **acidosis:**

- 1074     ▪ You feel very weak or tired.
- 1075     ▪ You have unusual (not normal) muscle pain.
- 1076     ▪ You have trouble breathing.
- 1077     ▪ You have stomach pain with nausea and vomiting.
- 1078     ▪ You feel cold, especially in your arms and legs.
- 1079     ▪ You feel dizzy or lightheaded.
- 1080     ▪ You have a fast or irregular heartbeat.

1081 • **Some people who have taken medicines like ATRIPLA have developed**  
1082 **serious liver problems called hepatotoxicity**, with liver enlargement  
1083 (hepatomegaly) and fat in the liver (steatosis). **Call your healthcare**  
1084 **provider right away if you get the following signs or symptoms of liver**  
1085 **problems:**

- 1086     ▪ Your skin or the white part of your eyes turns yellow (jaundice).
- 1087     ▪ Your urine turns dark.
- 1088     ▪ Your bowel movements (stools) turn light in color.
- 1089     ▪ You don't feel like eating food for several days or longer.
- 1090     ▪ You feel sick to your stomach (nausea).
- 1091     ▪ You have lower stomach area (abdominal) pain.

- 1092 • **You may be more likely to get lactic acidosis or liver problems** if you are  
1093 female, very overweight (obese), or have been taking nucleoside analog-  
1094 containing medicines, like ATRIPLA, for a long time.
- 1095 • **If you also have Hepatitis B Virus (HBV) infection and you stop taking**  
1096 **ATRIPLA, you may get a “flare-up” of your hepatitis. A “flare-up” is**  
1097 **when the disease suddenly returns in a worse way than before.** Patients  
1098 with HBV who stop taking ATRIPLA need close medical follow-up for several  
1099 months, including medical exams and blood tests to check for hepatitis that  
1100 could be getting worse. ATRIPLA is not approved for the treatment of HBV,  
1101 so you must discuss your HBV therapy with your healthcare provider.

## 1102 **What is ATRIPLA?**

1103 ATRIPLA contains 3 medicines, SUSTIVA<sup>®</sup> (efavirenz), EMTRIVA<sup>®</sup>  
1104 (emtricitabine) and VIREAD<sup>®</sup> (tenofovir disoproxil fumarate also called tenofovir  
1105 DF) combined in one pill. EMTRIVA and VIREAD are HIV (human  
1106 immunodeficiency virus) nucleoside analog reverse transcriptase inhibitors  
1107 (NRTIs) and SUSTIVA is an HIV non-nucleoside analog reverse transcriptase  
1108 inhibitor (NNRTI). VIREAD and EMTRIVA are the components of TRUVADA<sup>®</sup>.  
1109 ATRIPLA can be used alone as a complete regimen, or in combination with other  
1110 anti-HIV medicines to treat people with HIV infection. ATRIPLA is for adults age  
1111 18 and over. ATRIPLA has not been studied in children under age 18 or adults  
1112 over age 65.

1113 HIV infection destroys CD4 (T) cells, which are important to the immune system.  
1114 The immune system helps fight infection. After a large number of T cells are  
1115 destroyed, acquired immune deficiency syndrome (AIDS) develops.

1116 ATRIPLA helps block HIV reverse transcriptase, a viral chemical in your body  
1117 (enzyme) that is needed for HIV to multiply. ATRIPLA lowers the amount of HIV  
1118 in the blood (viral load). ATRIPLA may also help to increase the number of T  
1119 cells (CD4 cells), allowing your immune system to improve. Lowering the  
1120 amount of HIV in the blood lowers the chance of death or infections that happen  
1121 when your immune system is weak (opportunistic infections).

## 1122 **Does ATRIPLA cure HIV-1 or AIDS?**

1123 **ATRIPLA does not cure HIV infection or AIDS.** The long-term effects of  
1124 ATRIPLA are not known at this time. People taking ATRIPLA may still get  
1125 opportunistic infections or other conditions that happen with HIV infection.  
1126 Opportunistic infections are infections that develop because the immune system  
1127 is weak. Some of these conditions are pneumonia, herpes virus infections, and  
1128 *Mycobacterium avium complex* (MAC) infection. **It is very important that you**  
1129 **see your healthcare provider regularly while taking ATRIPLA.**

1130 **Does ATRIPLA reduce the risk of passing HIV-1 to others?**

1131 **ATRIPLA has not been shown to lower your chance of passing HIV to other**  
1132 **people through sexual contact, sharing needles, or being exposed to your**  
1133 **blood.**

- 1134 • **Do not share needles or other injection equipment.**
- 1135 • **Do not share personal items that can have blood or body fluids on them,**  
1136 **like toothbrushes or razor blades.**
- 1137 • **Do not have any kind of sex without protection.** Always practice safer sex  
1138 by using a latex or polyurethane condom or other barrier to reduce the  
1139 chance of sexual contact with semen, vaginal secretions, or blood.

1140 **Who should not take ATRIPLA?**

1141 Together with your healthcare provider, you need to decide whether ATRIPLA is  
1142 right for you.

1143 Do not take ATRIPLA if you are allergic to ATRIPLA or any of its ingredients.  
1144 The active ingredients of ATRIPLA are efavirenz, emtricitabine, and tenofovir DF.  
1145 See the end of this leaflet for a complete list of ingredients.

1146 **What should I tell my healthcare provider before taking ATRIPLA?**

1147 **Tell your healthcare provider if you:**

- 1148 • **Are pregnant or planning to become pregnant** (see “What should I avoid  
1149 while taking ATRIPLA?”).
- 1150 • **Are breastfeeding** (see “What should I avoid while taking ATRIPLA?”).
- 1151 • **Have kidney problems or are undergoing kidney dialysis treatment.**
- 1152 • **Have bone problems.**
- 1153 • **Have liver problems, including Hepatitis B Virus infection.** Your  
1154 healthcare provider may want to do tests to check your liver while you take  
1155 ATRIPLA.
- 1156 • **Have ever had mental illness or are using drugs or alcohol.**
- 1157 • **Have ever had seizures or are taking medicine for seizures.**

1158 **What important information should I know about taking other medicines**  
1159 **with ATRIPLA?**

1160 **ATRIPLA may change the effect of other medicines, including the ones for**  
1161 **HIV, and may cause serious side effects.** Your healthcare provider may  
1162 change your other medicines or change their doses. Other medicines, including  
1163 herbal products, may affect ATRIPLA. For this reason, **it is very important to**  
1164 **let all your healthcare providers and pharmacists know what medications, herbal**  
1165 **supplements, or vitamins you are taking.**

1166 **MEDICINES YOU SHOULD NOT TAKE WITH ATRIPLA**

1167 • The following medicines may cause serious and life-threatening side effects  
1168 when taken with ATRIPLA. You should not take any of these medicines while  
1169 taking ATRIPLA: Hismanal (astemizole), Vascor (bepridil), Propulsid  
1170 (cisapride), Versed (midazolam), Orap (pimozide), Halcion (triazolam), ergot  
1171 medications (for example, Wigraine and Cafergot).

1172 • ATRIPLA also should not be used with Combivir (lamivudine/zidovudine),  
1173 EMTRIVA, Epivir, Epivir-HBV (lamivudine), Epzicom (abacavir  
1174 sulfate/lamivudine), Trizivir (abacavir sulfate/lamivudine/zidovudine),  
1175 SUSTIVA, TRUVADA, or VIREAD.

1176 • Vfend (voriconazole) should not be taken with ATRIPLA since it may lose its  
1177 effect or may increase the chance of having side effects from ATRIPLA.

1178 It is also important to tell your healthcare provider if you are taking any of the  
1179 following:

1180 • Fortovase, Invirase (saquinavir), Biaxin (clarithromycin); or Sporanox  
1181 (itraconazole); **these medicines may need to be replaced with another**  
1182 **medicine when taken with ATRIPLA.**

1183 • Calcium channel blockers such as Cardizem or Tiazac (diltiazem), Covera HS  
1184 or Isoptin (verapamil) and others; Crixivan (indinavir); Methadone; Mycobutin  
1185 (rifabutin); Rifampin; cholesterol-lowering medicines such as Lipitor  
1186 (atorvastatin), Pravachol (pravastatin sodium), and Zocor (simvastatin); or  
1187 Zoloft (sertraline); **these medicines may need to have their dose changed**  
1188 **when taken with ATRIPLA.**

1189 • Videx, Videx EC (didanosine); tenofovir DF (a component of ATRIPLA) may  
1190 increase the amount of didanosine in your blood, which could result in more  
1191 side effects. **You may need to be monitored more carefully** if you are  
1192 taking ATRIPLA and didanosine together. Also, the dose of didanosine may  
1193 need to be changed.

1194 • Reyataz (atazanavir sulfate) or Kaletra (lopinavir/ritonavir); these medicines  
1195 may increase the amount of tenofovir DF (a component of ATRIPLA) in your  
1196 blood, which could result in more side effects. **You may need to be**  
1197 **monitored more carefully** if you are taking ATRIPLA and either Reyataz or  
1198 Kaletra together. Also, the dose of Reyataz or Kaletra may need to be  
1199 changed.

1200 • Medicine for seizures [for example, Dilantin (phenytoin), Tegretol  
1201 (carbamazepine), or phenobarbital]; your healthcare provider may want to  
1202 switch you to another medicine or check drug levels in your blood from time to  
1203 time.

1204 • **Taking St. John's wort (*Hypericum perforatum*), or products containing**  
1205 **St. John's wort with ATRIPLA is not recommended.** St. John's wort is a  
1206 herbal product sold as a dietary supplement. Talk with your healthcare

1207 provider if you are taking or are planning to take St. John's wort. Taking  
1208 St. John's wort may decrease ATRIPLA levels and lead to increased viral  
1209 load and possible resistance to ATRIPLA or cross-resistance to other anti-HIV  
1210 drugs.

1211 **These are not all the medicines that may cause problems if you take**  
1212 **ATRIPLA. Be sure to tell your healthcare provider about all medicines that**  
1213 **you take.**

1214 Keep a complete list of all the prescription and nonprescription medicines as well  
1215 as any herbal remedies that you are taking, how much you take, and how often  
1216 you take them. Make a new list when medicines or herbal remedies are added  
1217 or stopped, or if the dose changes. Give copies of this list to all of your  
1218 healthcare providers and pharmacists **every** time you visit your healthcare  
1219 provider or fill a prescription. This will give your healthcare provider a complete  
1220 picture of the medicines you use. Then he or she can decide the best approach  
1221 for your situation.

1222 **How should I take ATRIPLA?**

- 1223 • Take the exact amount of ATRIPLA your healthcare provider prescribes.  
1224 Never change the dose on your own. Do not stop this medicine unless your  
1225 healthcare provider tells you to stop.
- 1226 • You should take ATRIPLA on an empty stomach.
- 1227 • Swallow ATRIPLA with water.
- 1228 • Taking ATRIPLA at bedtime may make some side effects less bothersome.
- 1229 • Do not miss a dose of ATRIPLA. If you forget to take ATRIPLA, take the  
1230 missed dose right away, unless it is almost time for your next dose. Do not  
1231 double the next dose. Carry on with your regular dosing schedule. If you  
1232 need help in planning the best times to take your medicine, ask your  
1233 healthcare provider or pharmacist.
- 1234 • If you believe you took more than the prescribed amount of ATRIPLA, contact  
1235 your local poison control center or emergency room right away.
- 1236 • Tell your healthcare provider if you start any new medicine or change how  
1237 you take old ones. Your doses may need adjustment.
- 1238 • When your ATRIPLA supply starts to run low, get more from your healthcare  
1239 provider or pharmacy. This is very important because the amount of virus in  
1240 your blood may increase if the medicine is stopped for even a short time. The  
1241 virus may develop resistance to ATRIPLA and become harder to treat.
- 1242 • Your healthcare provider may want to do blood tests to check for certain side  
1243 effects while you take ATRIPLA.

1244 **What should I avoid while taking ATRIPLA?**

- 1245 • **Women taking ATRIPLA should not become pregnant.** Serious birth  
1246 defects have been seen in the babies of animals and women treated with  
1247 efavirenz (a component of ATRIPLA) during pregnancy. It is not known  
1248 whether efavirenz caused these defects. **Tell your healthcare provider**  
1249 **right away if you are pregnant.** Also talk with your healthcare provider if  
1250 you want to become pregnant.
- 1251 • Women should not rely only on hormone-based birth control, such as pills,  
1252 injections, or implants, because ATRIPLA may make these contraceptives  
1253 ineffective. Women must use a reliable form of barrier contraception, such as  
1254 a condom or diaphragm, even if they also use other methods of birth control.
- 1255 • **Do not breast-feed if you are taking ATRIPLA.** The Centers for Disease  
1256 Control and Prevention recommend that mothers with HIV not breast-feed  
1257 because they can pass the HIV through their milk to the baby. Also,  
1258 ATRIPLA may pass through breast milk and cause serious harm to the baby.  
1259 Talk with your healthcare provider if you are breast-feeding. You should stop  
1260 breast-feeding or may need to use a different medicine.
- 1261 • Taking ATRIPLA with alcohol or other medicines causing similar side effects  
1262 as ATRIPLA, such as drowsiness, may increase those side effects.
- 1263 • Do not take any other medicines, including prescription and nonprescription  
1264 medicines and herbal products, without checking with your healthcare  
1265 provider.
- 1266 • **Avoid doing things that can spread HIV infection** since ATRIPLA does not  
1267 stop you from passing the HIV infection to others.

1268 **What are the possible side effects of ATRIPLA?**

1269 **ATRIPLA may cause the following serious side effects:**

- 1270 • **Lactic acidosis** (buildup of an acid in the blood). Lactic acidosis can be a  
1271 medical emergency and may need to be treated in the hospital. **Call your**  
1272 **healthcare provider right away if you get signs of lactic acidosis.** (See  
1273 “What is the most important information I should know about ATRIPLA?”)
- 1274 • **Serious liver problems (hepatotoxicity)**, with liver enlargement  
1275 (hepatomegaly) and fat in the liver (steatosis). Call your healthcare provider  
1276 right away if you get any signs of liver problems. (See “What is the most  
1277 important information I should know about ATRIPLA?”)
- 1278 • **“Flare-ups” of Hepatitis B Virus (HBV) infection**, in which the disease  
1279 suddenly returns in a worse way than before, can occur if you have HBV and  
1280 you stop taking ATRIPLA. Your healthcare provider will monitor your  
1281 condition for several months after stopping ATRIPLA if you have both HIV  
1282 and HBV infection and may recommend treatment for your HBV.

1283 • **Serious psychiatric problems.** A small number of patients may experience  
1284 severe depression, strange thoughts, or angry behavior while taking  
1285 ATRIPLA. Some patients have thoughts of suicide and a few have actually  
1286 committed suicide. These problems may occur more often in patients who  
1287 have had mental illness. Contact your healthcare provider right away if you  
1288 think you are having these psychiatric symptoms, so your healthcare provider  
1289 can decide if you should continue to take ATRIPLA.

1290 • **Kidney problems.** If you have had kidney problems in the past or take other  
1291 medicines that can cause kidney problems, your healthcare provider should  
1292 do regular blood tests to check your kidneys.

1293 • **Changes in bone mineral density (thinning bones).** It is not known  
1294 whether long-term use of ATRIPLA will cause damage to your bones. If you  
1295 have had bone problems in the past, your healthcare provider may need to do  
1296 tests to check your bone mineral density or may prescribe medicines to help  
1297 your bone mineral density.

1298 **Common side effects:**

1299 Patients may have dizziness, headache, trouble sleeping, drowsiness, trouble  
1300 concentrating, and/or unusual dreams during treatment with ATRIPLA. These  
1301 side effects may be reduced if you take ATRIPLA at bedtime on an empty  
1302 stomach. They also tend to go away after you have taken the medicine for a few  
1303 weeks. If you have these common side effects, such as dizziness, it does not  
1304 mean that you will also have serious psychiatric problems, such as severe  
1305 depression, strange thoughts, or angry behavior. Tell your healthcare provider  
1306 right away if any of these side effects continue or if they bother you. It is possible  
1307 that these symptoms may be more severe if ATRIPLA is used with alcohol or  
1308 mood altering (street) drugs.

1309 If you are dizzy, have trouble concentrating, or are drowsy, avoid activities that  
1310 may be dangerous, such as driving or operating machinery.

1311 Rash may be common. Rashes usually go away without any change in  
1312 treatment. In a small number of patients, rash may be serious. If you develop a  
1313 rash, call your healthcare provider right away.

1314 Other common side effects include tiredness, upset stomach, vomiting, gas, and  
1315 diarrhea.

1316 **Other possible side effects with ATRIPLA include:**

1317 • Changes in body fat. Changes in body fat develop in some patients taking  
1318 anti-HIV medicine. These changes may include an increased amount of fat in  
1319 the upper back and neck ("buffalo hump"), in the breasts, and around the  
1320 trunk. Loss of fat from the legs, arms, and face may also happen. The cause  
1321 and long-term health effects of these fat changes are not known.

1322 • Skin discoloration (small spots or freckles) may also happen with ATRIPLA.

1323 Tell your healthcare provider or pharmacist if you notice any side effects while  
1324 taking ATRIPLA.

1325 Contact your healthcare provider before stopping ATRIPLA because of side  
1326 effects or for any other reason.

1327 This is not a complete list of side effects possible with ATRIPLA. Ask your  
1328 healthcare provider or pharmacist for a more complete list of side effects of  
1329 ATRIPLA and all the medicines you will take.

### 1330 **How do I store ATRIPLA?**

1331 • **Keep ATRIPLA and all other medicines out of reach of children.**

1332 • Store ATRIPLA at room temperature 77 °F (25 °C).

1333 • Keep ATRIPLA in its original container and keep the container tightly closed.

1334 • Do not keep medicine that is out of date or that you no longer need. If you  
1335 throw any medicines away make sure that children will not find them.

### 1336 **General information about ATRIPLA:**

1337 Medicines are sometimes prescribed for conditions that are not mentioned in  
1338 patient information leaflets. Do not use ATRIPLA for a condition for which it was  
1339 not prescribed. Do not give ATRIPLA to other people, even if they have the  
1340 same symptoms you have. It may harm them.

1341 This leaflet summarizes the most important information about ATRIPLA. If you  
1342 would like more information, talk with your healthcare provider. You can ask your  
1343 healthcare provider or pharmacist for information about ATRIPLA that is written  
1344 for health professionals.

1345 Do not use ATRIPLA if the seal over bottle opening is broken or missing.

### 1346 **What are the ingredients of ATRIPLA?**

1347 **Active Ingredients:** efavirenz, emtricitabine, and tenofovir disoproxil fumarate

1348 **Inactive Ingredients:** croscarmellose sodium, hydroxypropyl cellulose,  
1349 microcrystalline cellulose, magnesium stearate, sodium lauryl sulfate. The film  
1350 coating contains black iron oxide, polyethylene glycol, polyvinyl alcohol, red iron  
1351 oxide, talc, and titanium dioxide.

### 1352 **R Only**

1353 February 2008

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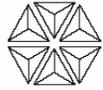
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