

DATA SHEET

ATRIPLA[®] (tenofovir disoproxil fumarate, emtricitabine and efavirenz) tablets

NAME OF THE MEDICINE

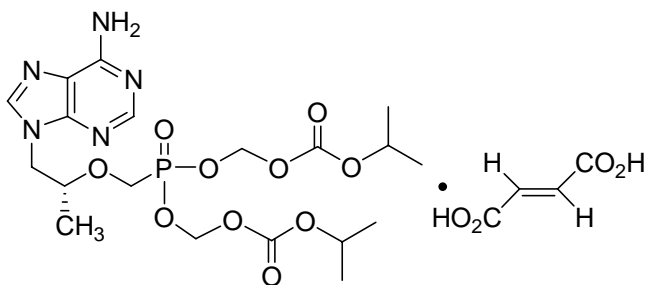
ATRIPLA (300 mg tenofovir disoproxil fumarate/200 mg emtricitabine/600 mg efavirenz) tablets.

The active substances in ATRIPLA tablets are tenofovir disoproxil fumarate (tenofovir DF), emtricitabine and efavirenz.

VIREAD[®] is the brand name for tenofovir DF, which is converted *in vivo* to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate. EMTRIVA[®] is the brand name for emtricitabine (FTC), a synthetic nucleoside analog of cytidine. STOCRIN[®] is the brand name for efavirenz, a non-nucleoside reverse transcriptase inhibitor. All three compounds exhibit activity against HIV-1 reverse transcriptase. Tenofovir DF and emtricitabine are the components of TRUVADA[®].

DESCRIPTION

Tenofovir disoproxil fumarate: Tenofovir DF is a fumaric acid salt of the *bis*-isopropoxycarbonyloxymethyl ester derivative of tenofovir. The chemical name of tenofovir DF is 9-[(*R*)-2 [[bis[[isopropoxycarbonyl]oxy] methoxy]phosphinyl]methoxy]propyl]adenine fumarate (1:1). It has a molecular formula of C₁₉H₃₀N₅O₁₀P • C₄H₄O₄ and a molecular weight of 635.52. It has the following structural formula:



CAS registry number: 202138-50-9

Tenofovir DF is a white to off-white crystalline powder with a solubility of 13.4 mg/mL in water at 25 °C. The partition coefficient (*log p*) for tenofovir disoproxil is 1.25 and the pK_a is 3.75.

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

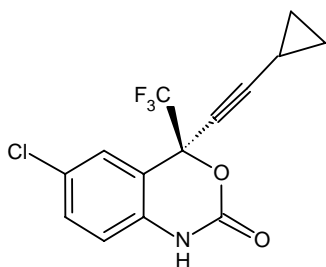
It has a molecular formula of C₈H₁₀FN₃O₃S and a molecular weight of 247.24. It has the following structural formula:



CAS registry number: 143491-57-0

Emtricitabine is a white to off-white crystalline powder with a solubility of approximately 112 mg/mL in water at 25 °C. The partition coefficient ($\log p$) for emtricitabine is -0.43 and the pKa is 2.65.

Efavirenz: The chemical name of efavirenz is (*S*)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2*H*-3,1-benzoxazin-2-one. It has a molecular formula of C₁₄H₉ClF₃NO₂ and a molecular weight of 315.68. It has the following structural formula:



CAS registry number: 154598-52-4

Efavirenz is a white to slightly pink crystalline powder. It is practically insoluble in water (<10 µg/mL).

ATRIPLA tablets contain the following ingredients as excipients:

Tablet core: Croscarmellose sodium, hydroxypropylcellulose, magnesium stearate, microcrystalline cellulose and sodium lauryl sulfate. *Film-coating:* Iron oxide black, iron oxide red, macrogol, poly(vinyl alcohol), talc and titanium dioxide.

Each ATRIPLA tablet is capsule shaped and pink in colour. Each tablet is debossed with '123' on one side and plain on the other side. The tablets are supplied in bottles with screw cap closures.

PHARMACOLOGY

Pharmacotherapeutic group: Antivirals for treatment of HIV infections, combinations, ATC code: J05AR06.

Mechanism of action

Tenofovir disoproxil fumarate: is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir DF requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of human immunodeficiency virus-type 1 (HIV-1) reverse

transcriptase (RT) by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into deoxyribonucleic acid (DNA), by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α , β , and mitochondrial DNA polymerase γ .

Emtricitabine: a synthetic nucleoside analog of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 RT by competing with the natural substrate deoxycytidine 5'-triphosphate by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine 5'-triphosphate is a weak inhibitor of mammalian DNA polymerases α , β , ϵ and mitochondrial DNA polymerase γ .

Efavirenz: is a selective non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1 RT with respect to template, primer or nucleoside triphosphates, with a small component of competitive inhibition. Human immunodeficiency virus-type 2 (HIV-2) RT and human cellular DNA polymerases (α , β , γ , and δ) are not inhibited by concentrations of efavirenz well in excess of those achieved clinically.

Antiviral activity *in vitro*

Tenofovir disoproxil fumarate, emtricitabine and efavirenz: In combination studies evaluating the *in vitro* antiviral activity of emtricitabine and efavirenz together, efavirenz and tenofovir together and emtricitabine and tenofovir together, additive to synergistic antiviral effects were observed.

Tenofovir disoproxil fumarate: The *in vitro* antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The IC_{50} (50% inhibitory concentration) values for tenofovir were in the range of 0.04 to 8.5 μ M. In drug combination studies of tenofovir with nucleoside analogue reverse transcriptase inhibitors (NRTIs) (abacavir, didanosine, lamivudine (3TC), stavudine (d4T), zalcitabine, zidovudine (AZT)), NNRTIs (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Tenofovir displayed antiviral activity *in vitro* against HIV-1 clades A, B, C, D, E, F, G and O (IC_{50} values ranged from 0.5 to 2.2 μ M). In addition, tenofovir has also been shown to be active *in vitro* against HIV-2, with similar potency as observed against HIV-1.

Emtricitabine: The *in vitro* antiviral activity of emtricitabine against laboratory and clinical isolates of HIV was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. The IC_{50} value for emtricitabine was in the range of 0.0013 to 0.64 μ M (0.0003 to 0.158 μ g/mL). In drug combination studies of emtricitabine with NRTIs (abacavir, 3TC, d4T, zalcitabine, AZT), NNRTIs (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Emtricitabine displayed antiviral activity *in vitro* against HIV-1 clades A, C, D, E, F, and G (IC_{50} values ranged from 0.007 to 0.075 μ M) and showed strain specific activity against HIV-2 (IC_{50} values ranged from 0.007 to 1.5 μ M).

Efavirenz: The *in vitro* antiviral activity of efavirenz was assessed in lymphoblastoid cell lines, peripheral blood mononuclear cells (PBMCs) and macrophage/monocyte cultures enriched from PBMCs. The 90 to 95% inhibitory concentration (IC₉₀ to IC₉₅) of efavirenz for wild-type laboratory adapted strains and clinical isolates ranged from 1.7 to less than or equal to 25 nM. Efavirenz demonstrated synergistic activity in cell culture in combination with the NRTIs AZT or didanosine, or the protease inhibitor, indinavir.

Anti-Hepatitis B Virus Activity *In Vitro*

In vitro studies evaluating the HBV activity of ATRIPLA and efavirenz have not been conducted.

Tenofovir disoproxil fumarate and emtricitabine: Tenofovir inhibits HBV production in HepG2 2.2.15 with an IC₅₀ value of 1.1 μM. Emtricitabine inhibits HBV production against laboratory strains of HBV with IC₅₀ values in the range of 0.01 to 0.04 μM.

Drug Resistance

Tenofovir disoproxil fumarate, emtricitabine and efavirenz: HIV isolates with reduced susceptibility to the combination of tenofovir, emtricitabine and efavirenz have been selected in cell culture and in clinical studies. Genotypic analysis of these isolates identified the K103N, M184V/I and/or the K65R amino acid substitutions in the viral RT.

Tenofovir disoproxil fumarate: HIV-1 isolates with reduced susceptibility to tenofovir have been selected *in vitro*. These viruses expressed a K65R mutation in reverse transcriptase and showed a 2 to 4 fold reduction in susceptibility to tenofovir.

Tenofovir-resistant isolates of HIV-1 have also been recovered from some patients treated with tenofovir DF in combination with other antiretroviral agents. In treatment-naïve patients treated with tenofovir DF + 3TC + efavirenz through 144 weeks, viral isolates from 8/47 (17%) patients with virologic failure showed reduced susceptibility to tenofovir. In treatment-naïve patients treated with tenofovir DF + emtricitabine + efavirenz through 144 weeks, none of the HIV isolates from 19 patients analyzed for resistance showed reduced susceptibility to tenofovir or the presence of the K65R mutation. In treatment-experienced patients, 14/304 (4.6%) of the tenofovir DF-treated patients with virologic failure showed reduced susceptibility to tenofovir. Genotypic analysis of the resistant isolates showed the K65R mutation in the HIV-1 reverse transcriptase gene.

Emtricitabine: Emtricitabine-resistant isolates of HIV have been selected *in vitro*. Genotypic analysis of these isolates showed that the reduced susceptibility to emtricitabine was associated with a mutation in the HIV reverse transcriptase gene at codon 184 which resulted in an amino acid substitution of methionine by valine or isoleucine (M184V/I).

Emtricitabine-resistant isolates of HIV have been recovered from some patients treated with emtricitabine alone or in combination with other antiretroviral agents. In a clinical study, viral isolates from 37.5% of treatment-naïve patients with virologic failure showed reduced susceptibility to emtricitabine. Genotypic analysis of these isolates showed that the resistance was due to M184V/I mutations in the HIV reverse transcriptase gene. In a second study in treatment-naïve patients, genotyping of viral isolates from 2/12 (17%) patients showed development of the M184V/I mutation.

Efavirenz: The potency of efavirenz in cell culture against viral variants with amino acid substitutions at positions 48, 108, 179, 181 or 236 in RT or variants with amino acid substitutions in the protease was similar to that observed against wild type viral strains. The single substitutions which led to the highest resistance to efavirenz in cell culture correspond to a leucine to isoleucine change at position 100 (L100I, 17 to 22-fold resistance) and a lysine to asparagine at position 103 (K103N, 18 to 33-fold resistance). Greater than 100-fold loss of susceptibility was observed against HIV variants expressing K103N in addition to other amino acid substitutions in RT. K103N was the most frequently observed RT substitution in viral isolates from patients who experienced a significant rebound in viral load during clinical studies of efavirenz in combination with indinavir or AZT + 3TC. This mutation was observed in 90% of patients receiving efavirenz with virological failure. Substitutions at RT positions 98, 100, 101, 108, 138, 188, 190 or 225 were also observed, but at lower frequencies, and often only in combination with K103N. The pattern of amino acid substitutions in RT associated with resistance to efavirenz was independent of the other antiviral medications used in combination with efavirenz.

In a clinical study of treatment-naïve patients (Study 934, see CLINICAL TRIALS) resistance analysis was performed on HIV isolates from all virologic failure patients with confirmed HIV RNA > 400 copies/ml at week 144 while on study drug or after treatment switch. Genotypic resistance to efavirenz, predominantly the K103N substitution, was the most common form of resistance that developed. Resistance to efavirenz occurred in 68% (13/19) analysed patients in the TRUVADA (tenofovir DF/emtricitabine) group and in 72% (21/19) analysed patients in the Combivir (zidovudine/lamivudine) group.

Cross-resistance: Cross-resistance among certain reverse transcriptase inhibitors has been recognized.

Tenofovir disoproxil fumarate: The K65R mutation selected by tenofovir is also selected in some HIV-1 infected subjects treated with abacavir, didanosine, or zalcitabine. HIV isolates with this mutation also show reduced susceptibility to emtricitabine and 3TC. Therefore, cross-resistance among these drugs may occur in patients whose virus harbours the K65R mutation. Patients with HIV-1 expressing three or more thymidine analogue associated mutations (TAMs) that included either the M41L or L210W reverse transcriptase mutation showed reduced susceptibility to tenofovir DF. Multinucleoside resistant HIV-1 with a T69S double insertion mutation in the reverse transcriptase showed reduced susceptibility to tenofovir.

Emtricitabine: Emtricitabine-resistant isolates (M184V/I) were cross-resistant to 3TC and zalcitabine but retained sensitivity to abacavir, didanosine, d4T, tenofovir, AZT, and NNRTIs (delavirdine, efavirenz, and nevirapine). HIV-1 isolates containing the K65R mutation, selected *in vivo* by abacavir, didanosine, tenofovir, and zalcitabine, demonstrated reduced susceptibility to inhibition by emtricitabine. Viruses harbouring mutations conferring reduced susceptibility to d4T and AZT (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) or didanosine (L74V) remained sensitive to emtricitabine. HIV-1 containing the K103N mutation associated with resistance to NNRTIs was susceptible to emtricitabine.

Efavirenz: Cross-resistance profiles for efavirenz, nevirapine and delavirdine in cell culture demonstrated that the K103N substitution confers loss of susceptibility to all three NNRTIs. Two of three delavirdine resistant clinical isolates examined were cross resistant to efavirenz and

contained the K103N substitution. A third isolate which carried a substitution at position 236 of RT was not cross resistant to efavirenz. Viral isolates recovered from PBMCs of patients enrolled in efavirenz clinical trials who showed evidence of treatment failure (viral load rebound) were assessed for susceptibility to NNRTIs. Thirteen isolates previously characterised as efavirenz resistant were also resistant to nevirapine and delavirdine. Five of these NNRTI resistant isolates were found to have K103N or a valine to isoleucine substitution at position 108 (V108I) in RT. Three of the efavirenz treatment failure isolates tested remained sensitive to efavirenz in cell culture and were also sensitive to nevirapine and delavirdine.

The potential for cross resistance between efavirenz and PIs is low because of the different enzyme targets involved. The potential for cross resistance between efavirenz and NRTIs is low because of the different binding sites on the target and mechanism of action.

Pharmacokinetics

One ATRIPLA tablet is bioequivalent to one VIREAD tablet (300 mg) plus one EMTRIVA capsule (200 mg) plus one STOCRIN tablet (600 mg) following single-dose administration in fasting healthy subjects (N=45).

The separate pharmaceutical forms of tenofovir DF, emtricitabine and efavirenz were used to determine the pharmacokinetics of tenofovir DF, emtricitabine and efavirenz in HIV infected patients.

Tenofovir disoproxil fumarate: The pharmacokinetic properties of tenofovir DF are summarized in Table 1. Following oral administration of tenofovir DF, maximum tenofovir serum concentrations are achieved in 1.0 ± 0.4 hour. *In vitro* binding of tenofovir to human plasma proteins is <0.7% and is independent of concentration over the range of 0.01 to 25 µg/mL. Approximately 70 to 80% of the intravenous dose of tenofovir is recovered as unchanged drug in the urine. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of tenofovir DF, the terminal elimination half-life of tenofovir is approximately 17 hours.

Table 1. Single Dose Pharmacokinetic Parameters for Tenofovir, Emtricitabine and Efavirenz in Adults¹

	<u>Tenofovir</u>	<u>Emtricitabine</u>	<u>Efavirenz</u>
Fasted Oral Bioavailability (%)	25	93	N/A
Plasma Terminal Elimination Half-Life (hr)	17	10	52 – 72
C _{max} (µg/mL)	0.30 ± 0.09	1.8 ± 0.7^2	$12.9^{2,3}$
AUC (µg*hr/mL)	2.29 ± 0.69	10.0 ± 3.1^2	$184^{2,3}$
CL/F (mL/min)	1043 ± 115	302 ± 94	N/A
CL _{renal} (mL/min)	243 ± 33	213 ± 89	N/A

1. Data presented as mean values.
 2. Data presented as steady state values.
 3. Data on 600 mg dose of efavirenz
- N/A Not Available

Emtricitabine: The pharmacokinetic properties of emtricitabine are summarized in Table 1. Following oral administration of emtricitabine 200 mg capsules, emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1 to 2 hours post-dose. *In vitro* binding of emtricitabine to human plasma proteins is <4% and is independent of concentration over the range of 0.02 to 200 µg/mL. Following administration of radiolabelled emtricitabine approximately 86% is recovered in the urine and 13% is recovered as metabolites. The metabolites of emtricitabine include 3'-sulfoxide diastereomers and their glucuronic acid conjugate. Emtricitabine is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of emtricitabine 200 mg capsules, the plasma emtricitabine half-life is approximately 10 hours.

Efavirenz: The pharmacokinetic properties of efavirenz are summarised in Table 1. In HIV infected patients, peak efavirenz plasma concentrations were attained by 5 hours and steady-state concentrations reached in 6 to 7 days. The steady state mean C_{max} , mean C_{min} and mean AUC were linear with 200 mg, 400 mg and 600 mg daily doses. In 35 patients receiving efavirenz 600 mg once daily, steady state C_{max} was 12.9 ± 3.4 µM [mean \pm S.D], steady state C_{min} was 5.6 ± 3.2 µM and AUC was 184 ± 72 µM·h.

Administration of a single 600 mg efavirenz tablet with a high fat/high caloric meal (approximately 1000 kcal, 500 to 600 kcal from fat) was associated with a 28% increase in mean $AUC_{0-\infty}$ of efavirenz and 79% increase in mean C_{max} of efavirenz relative to the exposures achieved when given under fasted conditions.

Efavirenz is highly bound (approximately 99.5 to 99.75%) to human plasma proteins, predominantly albumin. In HIV-1 infected patients (n=9) who received efavirenz 200 to 600 mg once daily for at least one month, cerebrospinal fluid concentrations ranged from 0.26 to 1.19% (mean 0.69%) of the corresponding plasma concentration. This proportion is approximately 3-fold higher than the non-protein-bound (free) fraction of efavirenz in plasma.

Studies in humans and *in vitro* studies using human liver microsomes have demonstrated that efavirenz is principally metabolised by the cytochrome P450 system to hydroxylated metabolites with subsequent glucuronidation of these hydroxylated metabolites. These metabolites are essentially inactive against HIV-1. The *in vitro* studies suggest that CYP3A4 and CYP2B6 are the major isozymes responsible for efavirenz metabolism. *In vitro* studies have shown that efavirenz inhibited P450 isozymes 2C9, 2C19 and 3A4 with K_i values (8.5 to 17 µM) in the range of observed efavirenz plasma concentrations. In *in vitro* studies, efavirenz did not inhibit CYP2E1 and inhibited CYP2D6 and CYP1A2 (K_i values 82 to 160 µM) only at concentrations well above those achieved clinically. Efavirenz has been shown to induce P450 enzymes resulting in the induction of its own metabolism. In uninfected volunteers multiple doses of 200 to 400 mg per day for 10 days resulted in a lower than predicted extent of accumulation (22 to 42% lower) and a shorter half-life.

Efavirenz has a relatively long terminal half-life of 52 to 76 hours after single doses and 40 to 55 hours after multiple doses. Approximately 14 to 34% of a radiolabelled dose of efavirenz was recovered in the urine and less than 1% of the dose was excreted in urine as unchanged efavirenz. Sixteen to 21% of efavirenz was recovered in the faeces. Nearly all of the urinary excretion of

radiolabelled drug was in the form of metabolites. Efavirenz accounted for the majority of the total radioactivity measured in faeces.

Effect of food

ATRIPLA has not been evaluated in the presence of food. Administration of a single 600 mg efavirenz tablet with a high fat/high caloric meal increased the mean AUC and C_{max} of efavirenz by 28% and 79%, respectively, compared to administration in the fasted state. Compared to fasted administration, dosing of tenofovir DF and emtricitabine in combination with either a high fat meal or a light meal increased the mean AUC and C_{max} of tenofovir by 35% and 15%, respectively, without affecting emtricitabine exposures.

Age and Gender

Children and Geriatric Patients: Pharmacokinetic studies with ATRIPLA have not been fully evaluated in children (<18 years) or in the elderly (over 65 years) (see PRECAUTIONS).

Gender: The pharmacokinetics of tenofovir DF, emtricitabine and efavirenz are similar in male and female patients.

Patients with Impaired Renal Function

ATRIPLA is not recommended for patients with moderate or severe renal impairment (creatinine clearance (CrCl) < 50 ml/min)). Patients with moderate or severe renal impairment require dose interval adjustment of emtricitabine and tenofovir DF that cannot be achieved with the combination tablet (see PRECAUTIONS).

Patients with Hepatic Impairment

The pharmacokinetics of ATRIPLA have not been studied in patients with hepatic impairment. ATRIPLA should be administered with caution to patients with liver disease due to the efavirenz component (see PRECAUTIONS).

Tenofovir disoproxil fumarate and emtricitabine: The pharmacokinetics of tenofovir following a 300 mg dose of tenofovir DF have been studied in non-HIV infected patients with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in patients with hepatic impairment compared with unimpaired patients. The pharmacokinetics of emtricitabine have not been studied in patients with moderate to severe hepatic impairment; however, emtricitabine is not significantly metabolized by liver enzymes, so the impact of liver impairment should be limited.

Efavirenz: The pharmacokinetics of efavirenz have not been adequately studied in patients with hepatic impairment (see PRECAUTIONS, Impaired liver function) and because of the extensive cytochrome P450 mediated metabolism of efavirenz, caution should be exercised in administering efavirenz to patients with liver disease.

CLINICAL TRIALS

The clinical experience of the combined use of the three agents is from studies with the separate pharmaceutical forms of tenofovir DF, emtricitabine and efavirenz within antiretroviral combination therapy. Clinical study 934, which demonstrated the safety and efficacy of tenofovir DF, emtricitabine and efavirenz in combination in antiretroviral treatment-naïve HIV-1 infected

patients, and clinical study 073 demonstrated the safety and efficacy of ATRIPLA in antiretroviral treatment experienced HIV-1 infected patients supports the use of ATRIPLA tablets for treatment of HIV-1 infection.

Study 934: Tenofovir DF + Emtricitabine + Efavirenz Compared with Combivir® (lamivudine / zidovudine) + Efavirenz

Study 934 is a randomized, open-label, active controlled multicentre study comparing two different dosing regimens in 511 antiretroviral-naïve patients. Patients were randomised to receive either EMTRIVA + VIREAD administered in combination with efavirenz or Combivir (lamivudine/zidovudine) administered in combination with efavirenz. For patients randomized to receive EMTRIVA + VIREAD the two drugs were administered individually for the first 96 weeks and then switched to TRUVADA (fixed dose combination) during weeks 96 to 144, without regard to food.

For inclusion in the study, antiretroviral treatment naïve adult patients (≥ 18 years) with plasma HIV RNA greater than 10,000 copies/mL, must have an estimated glomerular filtration rate as measured by Cockcroft-Gault method of ≥ 50 mL/min, adequate haematologic function, hepatic transaminases and alanine aminotransferases ≤ 3 ULN, total bilirubin ≤ 1.5 mg/dL, serum amylase ≤ 1.5 ULN and serum phosphorus ≥ 2.2 mg/dL. Exclusion criteria included: a new AIDS defining condition diagnosed within 30 days (except on the basis of CD4 criteria), ongoing therapy with nephrotoxic drugs or agents that interacted with efavirenz, pregnancy/lactation, a history of clinically significant renal / bone disease or malignant disease other than Kaposi's sarcoma or basal-cell carcinoma, or a life expectancy of less than one year. If efavirenz-associated central nervous system toxicities occurred, nevirapine could be substituted for efavirenz. Patients who were not receiving their originally assigned treatment regimen after week 48 or 96 and during the 30-day extension study window were not eligible to continue to weeks 96 or 144 respectively.

Patients had a mean age of 38 years (range 18 to 80), 86% were male, 59% were Caucasian and 23% were Black. The mean baseline CD4 cell count was 245 cells/mm³ (range 2 to 1191) and median baseline plasma HIV-1 RNA was 5.01 log₁₀ copies/mL (range 3.56 to 6.54). Patients were stratified by baseline CD4 count ($<$ or ≥ 200 cells/mm³); 41% had CD4 cell counts <200 cells/mm³ and 51% of patients had baseline viral loads $>100,000$ copies/mL. Treatment outcomes at 48 and 144 weeks for those patients who did not have efavirenz resistance at baseline are presented in Table 2.

Table 2. Outcomes of Randomised Treatment at Weeks 48 and 144 (Study 934) in Treatment Naïve Patients

Outcome at Weeks 48 and 144	WEEK 48		WEEK 144	
	EMTRIVA + VIREAD + EFV (N=244)	Combivir + EFV (N=243)	TRUVADA ⁴ + EFV (N=227)	Combivir + EFV (N=229)
Responder ¹	84%	73%	71%	58%
Virologic failure ²	2%	4%	3%	6%
Rebound	1%	3%	2%	5%
Never suppressed	0%	0%	0%	0%
Change in antiretroviral regimen	1%	1%	1%	1%
Death ³	<1%	1%	1%	1%

1. Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL.

2. Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL.

3. All deaths were unrelated to study drugs.

4. Patients received EMTRIVA + VIREAD up to week 96 and switched to TRUVADA from week 96 to 144.

In this study, tenofovir DF, emtricitabine and efavirenz in combination was statistically significantly superior to lamivudine/zidovudine in combination with efavirenz with regards to the primary and secondary endpoints: in achieving and maintaining HIV-1 RNA < 400 copies/mL through 48 and 144 weeks (Table 2). The difference in the proportions of responders between the tenofovir DF + emtricitabine group and the Combivir group was 11.4%, and the 95% CI was 4.3% to 18.6% (p=0.002) at week 48 and a difference of 12.9% (95% CI was 4.2% to 21.6%, p=0.004) at week 144.

Through 48 weeks of therapy, 80% and 70% of patients in the tenofovir DF + emtricitabine and the lamivudine/zidovudine arms, respectively, achieved and maintained HIV-1 RNA <50 copies/mL. The difference in the proportions of responders between the tenofovir DF + emtricitabine group and the Combivir group was 9.1%, and the 95% CI was 1.6% to 16.6% (p=0.021) at week 48. The proportion of patients responding at 144 weeks of therapy was higher in the TRUVADA group (64%) compared with the Combivir group (56%); p=0.082, a difference of 8.1% and the 95% CI was -0.8% to 17.0%.

The mean increase from baseline in CD4 cell count was 190 cells/mm³ and 312 cells/mm³ for the tenofovir DF + emtricitabine + efavirenz arm, and 158 cells/mm³ and 271 cells/mm³ for the Combivir + efavirenz arm (p=0.002 and p=0.088) at weeks 48 and 144 respectively.

Resistance analysis was performed on HIV isolates from all patients with > 400 copies/mL of HIV-1 RNA at week 144 while on study drug or after treatment switch. Genotypic resistance to efavirenz, predominantly the K103N mutation, was the most common form of resistance that developed in both treatment groups. Resistance to efavirenz occurred in 68% (13/19) analyzed patients in the TRUVADA group and in 72% (21/29) analyzed patients in the Combivir group.

The M184V mutation, associated with resistance to emtricitabine and 3TC, developed significantly less in the analysed patients in the TRUVADA group 11% (2/19) compared with the analysed patients in the Combivir group, 34% (10/29). Two patients in the Combivir group developed thymidine analog mutations, specifically D67N or K70R mutations in the reverse transcriptase gene. No patient in either treatment group developed the K65R mutation, which is associated with reduced susceptibility to VIREAD.

Study 073: ATRIPLA Compared to Stable Baseline Regimen (Combination Therapy)

Study 073 was a 48 week open-label, randomised clinical study in patients with stable, virologic suppression on combination antiretroviral therapy. The study compared the efficacy of ATRIPLA to antiretroviral therapy consisting of at least two nucleoside reverse transcriptase inhibitors (NRTIs) administered in combination with a protease inhibitor (with or without ritonavir) or a non-nucleoside reverse transcriptase inhibitor. At baseline, patients had been virologically suppressed (HIV-1 RNA < 200 copies/mL) on their current antiretroviral therapy for at least 12 weeks prior to study entry, and had no known HIV-1 substitutions conferring resistance to the components of ATRIPLA or history of virologic failure. Assessments were also included to evaluate change in HIV symptom index, quality of life, medication preference, and adherence.

Patients were randomised to switch to ATRIPLA (N=203) or stay on their baseline regimen (SBR) (N=97). Patients had a mean age of 43 years (range 22 to 73 years), 88% were male, 68% were white, 29% were black, and 3% were of other races. At baseline, median CD4 cell count was 516 cells/mm³ and all but 11 patients (3.7%) had HIV-1 RNA < 50 copies/mL. The median time since onset of antiretroviral therapy was three years.

Table 3 summarises treatment outcomes through Week 48.

Table 3. Outcomes of Randomised Treatment at Week 48 (Study 073)

Outcomes	ATRIPLA	Stayed on Baseline Regimen (SBR)
HIV-1 RNA < 200 copies/mL (TLOVR) ^a	89% (181/203)	88% (85/97)
HIV-1 RNA < 50 copies/mL	87% (177/203)	85% (82/97)
Median Change from Baseline in CD4 Cell Count (cells/mm ³)	+3	+9

a. Primary efficacy endpoint of this study was HIV-1 RNA <200 copies/mL at Week 48 based on TLOVR (time to loss of virological response) analysis.

The responder difference (HIV-1 RNA <200 copies/mL), ATRIPLA minus SBR, was 1% (95% CI: -7% to 9%, p=0.82) at week 48. ATRIPLA was non-inferior to SBR in this study.

There were no differences in HIV symptom index, quality of life and adherence between the ATRIPLA and the SBR group. Differences were reported in medication preference; the proportion of patients reporting they preferred ATRIPLA compared to their previous regimen increased from 64% at week 4 to 85% at week 48.

INDICATIONS

ATRIPLA is indicated for the treatment of HIV infected adults over the age of 18 years, alone or in combination with other antiretroviral agents.

CONTRAINDICATIONS

ATRIPLA is contraindicated in patients with known hypersensitivity to any of the active substances or any other component of the tablets.

ATRIPLA should not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, triazolam, pimozone, bepridil or ergot derivatives because competition for CYP3A4 by efavirenz could result in inhibition of metabolism of these drugs and create the potential for serious and/or life-threatening adverse events (eg. cardiac arrhythmias, prolonged sedation or respiratory depression).

ATRIPLA should not be administered concurrently with voriconazole because efavirenz significantly decreases voriconazole plasma concentrations (see DRUG INTERACTIONS).

PRECAUTIONS

ATRIPLA is a fixed-dose combination of tenofovir DF, emtricitabine and efavirenz and should not be administered concomitantly with other medicinal products containing any of the same active components, tenofovir DF, emtricitabine, efavirenz, with medicinal products containing lamivudine or with HEPSERA (adefovir dipivoxil).

General

Patients receiving ATRIPLA or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with HIV associated diseases.

Patients should be advised that antiretroviral therapies, including ATRIPLA, have not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions must continue to be used. Patients should also be informed that ATRIPLA is not a cure for HIV infection.

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported with the use of antiretroviral nucleoside analogues, including the tenofovir DF component of ATRIPLA, alone or in combination with other antiretrovirals, in the treatment of HIV infection. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogues to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with ATRIPLA should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Renal Impairment

The emtricitabine and tenofovir DF components of ATRIPLA are primarily excreted by the kidneys. Renal failure, renal impairment, elevated creatinine, hypophosphataemia and Fanconi syndrome have been reported with the use of tenofovir DF in clinical practice.

It is recommended that creatinine clearance is calculated in all patients prior to initiating therapy and, as clinically appropriate, during ATRIPLA therapy. Patients at risk for, or with a history of, renal dysfunction, including patients who have previously experienced renal events while receiving Hepsera, should be routinely monitored for changes in serum creatinine and phosphorus.

ATRIPLA is not recommended for patients with moderate or severe renal impairment (CrCl <50 mL/min). Patients with moderate or severe renal impairment require a dose adjustment of emtricitabine and tenofovir DF that cannot be achieved with the combination tablet.

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

Bone Effects

Bone toxicity including a reduction in bone mineral density was seen in animals following treatment with tenofovir or tenofovir DF. Clinically relevant bone abnormalities have not been seen in long term clinical studies (>3 years) with tenofovir DF. However, bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy (see ADVERSE EVENTS). If bone abnormalities are suspected during therapy then appropriate consultation should be obtained.

Liver Disease

Because of the extensive cytochrome P450 (CYP450)-mediated metabolism of efavirenz and limited clinical experience in patients with chronic liver disease, caution should be exercised in administering ATRIPLA to patients with liver disease. Patients should be monitored carefully for adverse events and, laboratory tests should be performed to evaluate their liver disease at periodic intervals.

In patients with known or suspected history of hepatitis B or C infection and in patients treated with other medications associated with liver toxicity monitoring of liver enzymes is recommended. A few of the postmarketing reports of hepatic failure occurred in patients with no pre-existing hepatic disease or other identifiable risk factors (see ADVERSE EVENTS). Liver enzyme monitoring should also be considered for patients without pre-existing hepatic dysfunction or other risk factors. In patients with persistent elevations of serum transaminases to greater than five times the upper limit of the normal range, the benefit of continued therapy with ATRIPLA needs to be weighed against the unknown risks of significant liver toxicity (see ADVERSE EVENTS).

HIV and Hepatitis B Virus (HBV) Co-infection

Discontinuation of ATRIPLA therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis due to the emtricitabine and tenofovir DF components of ATRIPLA. Patients co-infected with HIV and HBV who discontinue ATRIPLA should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of anti-hepatitis B therapy may be

warranted. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

Psychiatric Symptoms

Serious psychiatric adverse experiences including severe depression, suicidal ideation, nonfatal suicide attempts, aggressive behaviour, paranoid reactions and manic reactions have been reported in patients treated with efavirenz (see ADVERSE EVENTS). Patients with a history of psychiatric disorders appear to be at greater risk of these serious psychiatric adverse experiences. There have been occasional postmarketing reports of death by suicide, delusions and psychosis-like behaviour; although a causal relationship to the use of efavirenz cannot be determined from these reports. Patients should be advised that if they experience these symptoms they should contact their doctor immediately to assess the possibility that the symptoms may be related to the use of ATRIPLA, and if so, to determine whether the risks of continued therapy outweigh the benefits.

Nervous System Symptoms

Symptoms including, but were not limited to, dizziness, insomnia, somnolence, impaired concentration and abnormal dreaming are frequently reported adverse events in patients receiving efavirenz 600 mg daily in clinical studies (see ADVERSE EVENTS). Nervous System Symptoms usually begin during the first or second day of therapy and generally resolve after the first two to four weeks. Dosing at bedtime or on an empty stomach may improve the tolerability of these symptoms. Patients should be informed that these common nervous system symptoms are likely to improve with continued therapy and are not predictive of subsequent onset of any of the less frequent psychiatric symptoms. Patients receiving efavirenz should be alerted to the potential for additive central nervous system effects when efavirenz is used concomitantly with alcohol or psychoactive drugs.

Convulsions

Convulsions have been observed in patients receiving efavirenz, generally in the presence of a known medical history of seizures. Patients who are receiving concomitant anticonvulsant medications primarily metabolised by the liver, such as carbamazepine, phenytoin and phenobarbitone, may require periodic monitoring of plasma levels (see DRUG INTERACTIONS).

Skin Rash

Mild to moderate rash has been reported in clinical studies with efavirenz and usually resolves with continued therapy. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash. Severe rash associated with blistering, moist desquamation or ulceration has been reported in less than 1% of patients treated with efavirenz. The incidence of Grade 4 rashes (eg. erythema multiforme or Stevens-Johnson syndrome) was approximately 0.1%. The median time to onset of rash in adults was 11 days and the median duration was 16 days. Efavirenz should be discontinued if severe rash associated with blistering, desquamation, mucosal involvement or fever develops.

Rash was reported in 26 of 57 children (46%) treated with efavirenz during a 48-week period and was severe in three patients.

Lipodystrophy

Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors and lipoatrophy and nucleoside reverse transcriptase inhibitors has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including tenofovir DF, emtricitabine and efavirenz. In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of antiretroviral therapy. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Effect of Food

The administration of ATRIPLA with food may increase efavirenz exposure (see Pharmacokinetics) and may lead to an increase in frequency of undesirable effects. It is recommended that ATRIPLA be taken on an empty stomach, preferably at bedtime.

St John's Wort

Concomitant use of St. John's wort (*Hypericum perforatum*) or St. John's wort-containing products with ATRIPLA is not recommended since it is expected to result in reduced plasma concentrations of efavirenz. This effect is due to an induction of CYP3A4 and may result in a loss of therapeutic effect and development of resistance.

Drug Interactions and Other Forms of Interactions

General

No drug interaction studies have been conducted using ATRIPLA tablets. As ATRIPLA contains tenofovir DF, emtricitabine and efavirenz, any interactions that have been identified with these agents individually may occur with ATRIPLA.

Tenofovir disoproxil fumarate and Emtricitabine: Tenofovir and emtricitabine are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. No drug-drug interactions due to competition for renal excretion have been observed; however, co-administration of tenofovir DF and emtricitabine with drugs that are eliminated by active tubular secretion may increase serum concentrations of tenofovir, emtricitabine, and/or the co-administered drug. Drugs that decrease renal function may increase serum concentrations of tenofovir and/or emtricitabine.

No clinically significant drug interactions have been observed between tenofovir DF and abacavir, efavirenz, emtricitabine, indinavir, 3TC, lopinavir/ritonavir, methadone and oral contraceptives in studies conducted in healthy volunteers. In a study conducted in healthy volunteers dosed with a single 600 mg dose of ribavirin, no clinically significant drug interactions were observed between tenofovir DF and ribavirin. Similarly, no clinically significant drug interactions have been observed between emtricitabine and famciclovir, indinavir, stavudine, zidovudine and tenofovir DF.

Efavirenz: Efavirenz is an inducer of CYP3A4. Other compounds that are substrates of CYP3A4 may have decreased plasma concentrations when coadministered with efavirenz. In vitro studies have demonstrated that efavirenz inhibits P450 isozymes 2C9, 2C19, and 3A4 in the range of observed efavirenz plasma concentrations. Coadministration of ATRIPLA with drugs primarily metabolised by these isozymes may result in altered plasma concentrations of the coadministered drug. Drugs that induce CYP3A4 activity may be expected to increase the clearance of efavirenz.

ATRIPLA should not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, triazolam, pimozone, bepridil, voriconazole or ergot derivatives (see CONTRAINDICATIONS).

Concomitant Antiretroviral Agents:

Amprenavir: Although efavirenz (600 mg once daily) was seen to decrease the AUC, C_{max} and C_{min} of amprenavir (1200 mg every 12 hours) in HIV infected patients, the clinical significance of decreased amprenavir concentrations has not been established, the possibility of this interaction should be taken into consideration before choosing a regimen containing both efavirenz and amprenavir. When amprenavir is combined with ritonavir the effect of efavirenz is compensated by the pharmacokinetic booster effect of ritonavir. When efavirenz was given in combination with amprenavir (600 mg twice daily) and ritonavir (100 or 200 mg twice daily), no dosage adjustment was necessary.

Fosamprenavir calcium: Appropriate doses of fosamprenavir (unboosted) and ATRIPLA with respect to safety and efficacy have not been established. 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.

Atazanavir/ritonavir: Insufficient data are available to make a dosing recommendation for atazanavir/ritonavir in combination of ATRIPLA. Therefore coadministration of atazanavir/ritonavir and ATRIPLA is not recommended.

Coadministration of efavirenz 600 mg with atazanavir in combination with low dose ritonavir resulted in substantial decreases in atazanavir exposure, necessitating dosage adjustment of atazanavir. Tenofovir DF affects the pharmacokinetics of atazanavir (see Table 4). Tenofovir should only be administered with boosted atazanavir (ATZ 300 mg/RTV 100 mg). The safety and efficacy of this regimen has been substantiated over 48 weeks in a clinical study. When unboosted atazanavir (400 mg) was coadministered with tenofovir DF, atazanavir increased tenofovir C_{max} by 14% and AUC by 24%.

Indinavir: Insufficient data are available to make a dosing recommendation with ATRIPLA. When indinavir (800 mg every eight hours) was given with efavirenz, the indinavir AUC and C_{\max} were decreased by approximately 31 and 16%, respectively, as a result of enzyme induction. The optimal dose of indinavir, when given in combination with efavirenz, is not known. Increasing the indinavir dose to 1000 mg (every eight hours) does not compensate for the increased indinavir metabolism due to efavirenz. No adjustment of the dose of efavirenz is necessary when given with indinavir. While the clinical significance of decreased indinavir concentrations has not been established, the magnitude of the observed pharmacokinetic interaction should be taken into consideration when choosing a regimen containing both efavirenz and indinavir.

Lopinavir/ritonavir: Insufficient data are available to make a dosing recommendation with ATRIPLA. When tenofovir DF was administered with lopinavir (400 mg)/ritonavir (100 mg), the tenofovir AUC increased by 32%; no changes were observed in the pharmacokinetics of lopinavir and ritonavir. Coadministration of lopinavir/ritonavir with efavirenz resulted in a substantial decrease in lopinavir exposure, necessitating dosage adjustment of lopinavir/ritonavir. When used in combination with efavirenz and two NRTIs in multiple protease inhibitor experienced subjects, increasing the dose of lopinavir/ritonavir 33.3% from 400/100 mg (three soft capsules) twice daily, to 533/133 mg (four soft capsules) twice daily yielded similar lopinavir plasma concentrations as compared to historical data of lopinavir/ritonavir 400/100 mg twice daily.

Ritonavir: When efavirenz 600 mg (given once daily at bedtime) and ritonavir 500 mg (given every 12 hours) were studied in uninfected volunteers, the combination was not well tolerated and was associated with a higher frequency of adverse clinical experiences (eg, dizziness, nausea, paresthesia) and laboratory abnormalities (elevated liver enzymes).

Sufficient data on the tolerability of efavirenz with low-dose ritonavir (100 mg, once or twice daily) are not available. When using efavirenz in a regimen containing low-dose ritonavir, the possibility of an increase in the incidence of efavirenz-associated adverse events should be considered, namely due to possible pharmacodynamic interaction.

Monitoring of liver enzymes is recommended when ATRIPLA is used in combination with ritonavir.

Saquinavir: When saquinavir soft gelatin capsules (1,200 mg every eight hours) was given with efavirenz to uninfected volunteers, saquinavir AUC and C_{\max} were decreased by 62% and 50%, respectively. Saquinavir should not be used as sole protease inhibitor in combination with ATRIPLA. No data are available on the potential interactions of efavirenz with the combination of saquinavir and ritonavir.

Didanosine: Concomitant dosing of tenofovir DF with didanosine buffered tablets or enteric-coated capsules significantly increase the C_{\max} and AUC of didanosine. When didanosine 250 mg enteric-coated capsules were administered with tenofovir DF, systemic exposures of didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions. The mechanism of this interaction is unknown. Table 4 below, summarises the effects of tenofovir DF on the pharmacokinetics of didanosine.

As a result of this increased exposure, patients receiving ATRIPLA and didanosine should be carefully monitored for didanosine-associated adverse events, including pancreatitis, lactic acidosis and neuropathy. Suppression of CD4 cell counts has been observed in patients receiving tenofovir DF with didanosine at a dose of 400 mg daily. In adults weighing ≥ 60 kg, the didanosine dose should be reduced to 250 mg daily when it is coadministered with ATRIPLA. Data are not available to recommend a dose adjustment of didanosine for patients weighing < 60 kg. When coadministered, ATRIPLA and didanosine EC may be taken under fasted conditions or with a light meal (< 400 kcal, 20% fat). Coadministration of didanosine buffered tablet formulation with ATRIPLA should be under fasted conditions. **Coadministration of ATRIPLA and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse events. Didanosine should be discontinued in patients who develop didanosine-associated adverse events.**

Table 4. Drug Interactions: Changes in Pharmacokinetic Parameters for Didanosine and Atazanavir in the Presence of Tenofovir DF

Co-administered Drug	Dose of Co-administered Drug (mg)	N	% Change of Co-administered Drug Pharmacokinetic Parameters ¹ (90% CI)		
			C _{max}	AUC	C _{min}
Didanosine ³ enteric-coated capsules	400 once / with or without food ²	26	↑ 48–64% (↑ 25–↑ 89)	↑ 48–60% (↑ 31–↑ 79)	NC
	250 once / Simultaneously with tenofovir DF, fasted ⁴	28	↔	↑ 14 (0–↑ 31)	NC
	250 once / Simultaneously with tenofovir DF, fed ^{2,4}	28	↓ 29 (↓ 39–↓ 18)	↓ 11 (↓ 23–↑ 2)	NC
Atazanavir sulfate ⁵	400 once daily x 14 days	34	↓ 21 (↓ 27 to ↓ 14)	↓ 25 (↓ 30 to ↓ 19)	↓ 40 (↓ 48 to ↓ 32)
	Atazanavir/Ritonavir ⁶ 300/100 once daily x 42 days	10	↓ 28 (↓ 50 to ↑ 5) ⁶	↓ 25 (↓ 42 to ↓ 3) ⁶	↓ 23 (↓ 46 to ↑ 10) ⁶

1. Increase = ↑; Decrease = ↓; No Effect = ↔; NC = Not Calculated
2. Administration with food was with a light meal (~373 kcal, 20% fat).
3. See PRECAUTIONS regarding use of didanosine with tenofovir disoproxil fumarate.
4. Relative to 400 mg alone, fasted.
5. Reyataz Prescribing Information (Bristol-Myers Squibb)
6. In HIV-infected patients, addition of tenofovir DF to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and C_{min} values of atazanavir that were 2.3- and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone (Reyataz March 2004 United States Package Insert)

Maraviroc:

The AUC₁₂ and C_{max} of maraviroc (100 mg twice daily) are decreased by 45% and 51%, respectively, when given with efavirenz (600 mg once daily) compared to maraviroc administered alone. Refer to the prescribing information for maraviroc for guidance on co-administration of efavirenz. (Maraviroc is currently not available in New Zealand).

Concomitant Antimicrobial Agents:

Macrolide Antibiotics:

Clarithromycin: Coadministration of efavirenz 400 mg once daily with clarithromycin given as 500 mg every 12 hours for seven days resulted in a significant effect of efavirenz on the pharmacokinetics of clarithromycin. The AUC and C_{max} of clarithromycin decreased 39 and 26%, respectively, while the AUC and C_{max} of the active clarithromycin hydroxymetabolite were increased 34 and 49%, respectively, when used in combination with efavirenz. The clinical significance of these changes in clarithromycin plasma levels is not known. In uninfected volunteers, 46% developed rash while receiving efavirenz and clarithromycin. No dose adjustment of efavirenz is recommended when given with clarithromycin. Alternatives to clarithromycin should be considered.

Rifamycins:

Rifabutin: Coadministration of rifabutin (300 mg once daily for 14 days) and efavirenz (600 mg once daily for 14 days) reduced rifabutin AUC and C_{max} by 38% and 32% respectively, in uninfected volunteers. The daily dose of rifabutin should be increased by 50% when coadministered with ATRIPLA. For regimens where rifabutin is given 2 or 3 times a week, a doubling of the rifabutin dose should be considered.

Rifampicin: Rifampicin reduced efavirenz AUC by 26% and C_{max} by 20% in uninfected volunteers. An additional 200 mg/day (total 800 mg/day) of efavirenz is recommended when rifampicin is coadministered with ATRIPLA.

Concomitant Antifungal Agents:

Itraconazole: Coadministration of efavirenz (600 mg once daily) with itraconazole (200 mg orally every 12 hours) in uninfected volunteers decreased the steady-state AUC, C_{max} and C_{min} of itraconazole by 39%, 37% and 44% respectively; and of hydroxyitraconazole by 37%, 35% and 43% respectively, compared to itraconazole administered alone. The pharmacokinetics of efavirenz were not affected. Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered.

Voriconazole: Voriconazole increased efavirenz AUC and C_{max} by 44% and 38%, respectively while efavirenz decreased voriconazole AUC and C_{max} by 77% and 61% respectively in uninfected volunteers. Coadministration of ATRIPLA and voriconazole is contraindicated (see CONTRAINDICATIONS).

Posaconazole: Co-administration of efavirenz (400 mg orally once daily) with posaconazole (400 mg orally twice daily) decreased the AUC and C_{max} of posaconazole by 50% and 45% respectively, compared to posaconazole administered alone. Concomitant use of posaconazole and ATRIPLA should be avoided unless the benefit to the patient outweighs the risk.

Concomitant Anticonvulsant Agents:

Carbamazepine: Coadministration of efavirenz (600 mg orally once daily) with carbamazepine (400 mg once daily) in uninfected volunteers resulted in a two-way interaction. The steady-state AUC, C_{max} and C_{min} of carbamazepine decreased by 27%, 20% and 35% respectively, while the steady-state AUC, C_{max} and C_{min} of efavirenz decreased by 36%, 21% and 47% respectively. The steady-state AUC, C_{max} and C_{min} of the active carbamazepine epoxide metabolite remained unchanged. Carbamazepine plasma levels should be monitored periodically. There are no data

with coadministration of higher doses of with medicinal product; therefore, no dose recommendation can be made, and alternative anticonvulsant treatment should be considered.

Other anticonvulsants: When efavirenz is administered concomitantly with phenytoin, phenobarbitone or other anticonvulsants that are substrates of CYP450 isozymes, there is the potential for reduction or increase in the plasma concentrations of each agent; therefore, periodic monitoring of plasma levels may be required.

Concomitant Lipid-Lowering Agents:

Coadministration of efavirenz with the HMG-CoA reductase inhibitors atorvastatin, pravastatin, or simvastatin has been shown to reduce the plasma concentration of the statin in uninfected volunteers. Dosage adjustments of statins may be required (refer to the data sheet for the statin).

Atorvastatin: Coadministration of efavirenz (600 mg orally once daily) with atorvastatin (10 mg orally once daily) in uninfected volunteers decreased the steady-state AUC and C_{max} of atorvastatin by 43% and 12%, respectively, of 2-hydroxy atorvastatin by 35% and 13% respectively, of 4-hydroxy atorvastatin by 4% and 47%, respectively, and of total active HMG-CoA reductase inhibitors by 34% and 20%, respectively, compared to atorvastatin administered alone.

Pravastatin: Coadministration of efavirenz (600 mg orally once daily) with pravastatin (40 mg orally once daily) in uninfected volunteers decreased the steady-state AUC and C_{max} of pravastatin by 40% and 18% respectively, compared to pravastatin administered alone.

Simvastatin: Coadministration of efavirenz (600 mg orally once daily) with simvastatin (40 mg orally once daily) in uninfected volunteers decreased the steady-state AUC and C_{max} of simvastatin by 69% and 76% respectively; of simvastatin acid by 58% and 51% respectively; of total active HMG-CoA reductase inhibitors by 60% and 62% respectively; of total HMG-CoA reductase inhibitors by 60% and 70% respectively compared to simvastatin administered alone.

Coadministration of efavirenz with atorvastatin, pravastatin or simvastatin did not affect the efavirenz AUC and C_{max} values. No dosage adjustment is necessary for efavirenz.

Concomitant Calcium Channel Blockers:

Diltiazem: Coadministration of efavirenz (600 mg orally once daily) with diltiazem (240 mg orally once daily) in uninfected volunteers decreased the steady-state AUC, C_{max} and C_{min} of diltiazem by 69%, 60% and 63% respectively; desacetyl diltiazem by 75%, 64% and 62% respectively and N-monodesmethyl diltiazem by 37%, 28% and 37% respectively, compared to diltiazem administered alone. Diltiazem dose adjustments should be guided by clinical response (refer to the data sheet for diltiazem). Pharmacokinetic parameters for efavirenz were slightly increased (11% to 16%). No dosage adjustment of efavirenz is necessary when administered with diltiazem.

Other calcium channel blockers: No data are available on the potential interactions of efavirenz with other calcium channel blockers that are substrates of CYP3A4 enzyme (e.g verapamil, felodipine, nifedipine). When efavirenz is administered concomitantly with one of these agents,

there is potential for reduction in the plasma concentrations of the calcium channel blocker. Dose adjustments should be guided by clinical response (refer to the data sheet for the calcium channel blocker).

Other Interactions:

Antidepressants:

Sertraline: Sertraline did not significantly alter the pharmacokinetics of efavirenz; however, efavirenz significantly decreased sertraline C_{max} , C_{24} and AUC by 29 to 46%. The dose of setraline should be increased when administered with ATRIPLA to compensate for the indication of setraline metabolism by efavirenz. Sertraline dose increases should be guided by clinical response.

Narcotic analgesics:

Methadone: Coadministration of efavirenz with methadone has resulted in decreased plasma levels of methadone and signs of opiate withdrawal in HIV-infected patients. Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.

Hormonal Contraceptives:

A reliable method of barrier contraception must be used in addition to hormonal contraceptives.

Oral: When an oral contraceptive (ethinyl estradiol 0.035 mg/norgestimate 0.25 mg once daily) and efavirenz (600 mg once daily) were co-administered for 14 days, efavirenz had no effect on ethinyl estradiol concentrations but plasma concentrations of norelgestromin and levonorgestrel, active metabolites of norgestimate, were markedly decreased in the presence of efavirenz (64%, 46%, and 82% decrease in norelgestromin AUC, C_{max} and C_{min} , respectively, and 83%, 80% and 86% decrease in levonorgestrel AUC, C_{max} and C_{min} , respectively). The clinical significance of these effects is not known. No effect of ethinylestradiol on efavirenz plasma concentrations was observed.

Injection: Limited information exists regarding efavirenz and injectable hormonal contraception. In a 3 month medicine interaction study of depo-medroxyprogesterone acetate (DMPA) and efavirenz, plasma progesterone levels for all subjects remained below 5 ng/mL, consistent with suppression of ovulation.

Implant: The interaction between etonogestrel and efavirenz has not been studied. Decreased exposure of etonogestrel may be expected (CYP3A4 induction), and there have been occasional post-marketing reports of contraceptive failure with etonogestrel in efavirenz-exposed patients.

St. John's wort (*Hypericum perforatum*): See PRECAUTIONS.

Cannabinoid test interaction. Efavirenz does not bind to cannabinoid receptors. False positive urine cannabinoid test results have been reported in uninfected volunteers who received efavirenz. False positive test results have only been observed with the CEDIA DAU Multilevel THC assay, which is used for screening, and have not been observed with other cannabinoid assays including tests used for confirmation of positive results.

Animal Toxicology

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

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

Carcinogenicity and Mutagenicity

No carcinogenicity studies have been conducted with tenofovir DF, emtricitabine and efavirenz in combination.

Tenofovir disoproxil fumarate: In a long-term carcinogenicity study conducted in mice with tenofovir DF there was a low incidence of duodenal tumours with the highest dose of 600 mg/kg/day. These were associated with a high incidence of duodenal mucosal hyperplasia, which was also observed with a dose of 300 mg/kg/day. These findings may be related to high local drug concentrations in the gastro-intestinal tract, likely to result in much higher exposure margins than that based on the AUC. At therapeutic doses the risk of these duodenal effects occurring in humans is likely to be low. The systemic drug exposure (AUC) with the 600 mg/kg/day dose was approximately 15 times the human exposure at the therapeutic dose of 300 mg/day. No tumourigenic response was observed in rats treated with doses of up to 300 mg/kg/day (5 times the human systemic exposure at the therapeutic dose based on AUC).

Tenofovir DF was mutagenic in an *in vitro* mouse L5178Y lymphoma cell assay (tk locus) and in an *ex vivo* assay for unscheduled DNA synthesis in rat hepatocytes, but it was negative in *in vitro* bacterial assays for gene mutation and an *in vivo* mouse micronucleus test for chromosomal damage.

Emtricitabine: In long-term oral carcinogenicity studies conducted with emtricitabine, no drug-related increases in tumour incidence were found in mice at doses up to 750 mg/kg/day (32 times the human systemic exposure (AUC) at the therapeutic dose of 200 mg/day) or in rats at doses up to 600 mg/kg/day (38 times the human systemic exposure at the therapeutic dose).

Emtricitabine was not mutagenic in bacteria or mouse lymphoma cell assays *in vitro* nor clastogenic in the mouse micronucleus test *in vivo*.

Efavirenz: Carcinogenicity studies using efavirenz showed an increased incidence of hepatic and pulmonary tumours in female mice, but not in male mice. The mechanism for tumour formation and the potential relevance for humans are not known. Carcinogenicity studies using efavirenz in male mice and in male and female rats were negative. Efavirenz was not genotoxic in assays for gene mutations (*S. typhimurium*, *E. coli* and Chinese hamster ovary cells) and chromosomal damage (human peripheral blood lymphocytes, Chinese hamster ovary cells, and a mouse

micronucleus assay). While the carcinogenic potential in humans is unknown, these data suggest that the clinical benefit of efavirenz outweighs the potential carcinogenic risk to humans.

Impairment of Fertility

No reproductive toxicity studies have been conducted with tenofovir DF, emtricitabine and efavirenz in combination.

Tenofovir disoproxil fumarate: Male and female rat fertility and mating performance or early embryonic development were unaffected by an oral tenofovir DF dose (600 mg/kg/day) that achieved systemic drug exposures that were in excess of the expected value in humans receiving the therapeutic dose (5-fold based on plasma AUC). There was, however, an alteration of the oestrous cycle in female rats.

Emtricitabine: Emtricitabine did not affect fertility in male rats or in female and male mice at respective approximate exposures (AUC) of 130 and 50 to 80 times the exposure in humans. The fertility of offspring was unaffected by treatment of mice from early gestation to the end of lactation (50 times the human exposure).

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

Use in Pregnancy

Pregnancy Category D

Efavirenz may cause foetal harm when administered during the first trimester to a pregnant women. Pregnancy should be avoided in women receiving ATRIPLA. Barrier contraception must always be used in combination with other methods of contraception (e.g. oral or other hormonal contraceptives). Women of childbearing potential should undergo pregnancy testing before initiation of ATRIPLA. If a woman takes ATRIPLA during the first trimester of pregnancy, or becomes pregnant whilst taking ATRIPLA, she should be informed of the potential harm to the foetus. Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of ATRIPLA is recommended.

There are no well controlled clinical studies of ATRIPLA in pregnant women. No embryofoetal development studies have been conducted with tenofovir DF, emtricitabine and efavirenz in combination. ATRIPLA should not be used during pregnancy unless the potential benefit to the mother clearly outweighs the potential risk to the foetus and there are no other appropriate treatment options.

In post-marketing experience through an antiretroviral pregnancy registry, more than 400 pregnancies with first-trimester exposure to efavirenz as part of a combination antiretroviral regimen have been reported with no specific malformation pattern. In this registry, a small number of cases of neural tube defects associated with efavirenz exposure, including meningomyelocele, have been reported; most of these reports were retrospective, and causality has not been established.

Efavirenz: Malformations have been observed in 3 of 20 fetuses/infants from efavirenz-treated cynomolgus monkeys (versus 0 of 20 concomitant controls) in a developmental toxicity study. The pregnant monkeys were dosed throughout pregnancy (postcoital days 20 to 150) with efavirenz 60 mg/kg daily, a dose which resulted in plasma drug concentrations similar to those seen in humans given 600 mg/day. Anencephaly and unilateral anophthalmia were observed in one foetus, microphthalmia was observed in another foetus, and cleft palate was observed in a third foetus. Efavirenz crosses the placenta in cynomolgus monkeys and produces foetal blood concentrations similar to maternal blood concentrations. Because teratogenic effects have been seen in primates at efavirenz exposures similar to those seen in the clinic at the recommended dose, pregnancy should be avoided in women receiving efavirenz.

Efavirenz has been shown to cross the placenta in rats and rabbits and produces foetal blood concentrations of efavirenz similar to maternal blood concentrations. An increase in foetal resorptions was observed in rats at efavirenz doses that produced peak plasma concentrations and AUC values in female rats equivalent to or lower than those achieved in humans given efavirenz 600 mg once daily. Efavirenz produced no reproductive toxicities when given to pregnant rabbits at doses that produced peak plasma concentrations similar to, and AUC values approximately half of, those achieved in humans when given efavirenz 600 mg once daily.

Use in Lactation

Studies in rats have demonstrated that efavirenz and tenofovir are excreted in milk; concentrations of efavirenz were eight times higher than those in maternal plasma.

It is not known whether efavirenz, emtricitabine or tenofovir are excreted in human milk. Because of the potential for both HIV transmission and for serious adverse events in nursing infants, mothers should be instructed not to breast feed if they are receiving ATRIPLA.

Use in Children

ATRIPLA is not recommended for use in children below 18 years of age due to insufficient data on safety and efficacy.

Use in the Elderly

Clinical studies of tenofovir DF, emtricitabine and efavirenz did not contain sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. Caution should be exercised when prescribing ATRIPLA to the elderly, keeping in mind the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Effects on ability to drive and use machines

ATRIPLA may cause dizziness, impaired concentration and/or drowsiness. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery.

ADVERSE EFFECTS

As ATRIPLA contains tenofovir DF, emtricitabine and efavirenz, adverse events associated with these individual antiretroviral agents may be expected to occur with the fixed combination tablet.

For additional safety information about VIREAD (tenofovir DF), EMTRIVA (emtricitabine) or STOCRIN (efavirenz) in combination with other antiretroviral agents, consult the data sheet for these products.

In addition to the adverse events in Study 934 (Table 5) and Study 073, the following adverse events were observed in clinical studies of tenofovir DF, emtricitabine or efavirenz in combination with other antiretroviral agents.

Tenofovir disoproxil fumarate: More than 12,000 patients have been treated with VIREAD alone or in combination with other antiretroviral medicinal products for periods of 28 days to 215 weeks in Phase I-III clinical trials and expanded access studies. A total of 1,544 patients have received VIREAD 300 mg once daily in Phase I-III clinical trials; over 11,000 patients have received VIREAD in expanded access studies.

The most common adverse events that occurred in patients receiving VIREAD with other antiretroviral agents in clinical trials were mild to moderate gastrointestinal events, such as nausea, diarrhoea, vomiting and flatulence.

Emtricitabine: More than 2000 adult patients with HIV infection have been treated with EMTRIVA alone or in combination with other antiretroviral agents for periods of 10 days to 200 weeks in Phase I-III clinical trials.

Assessment of adverse reactions is based on data from studies 301A and 303 in which 571 treatment naïve (301A) and 440 treatment experienced (303) patients received EMTRIVA 200 mg (n=580) or comparator drug (n=431) for 48 weeks.

The most common adverse events that occurred in patients receiving EMTRIVA with other antiretroviral agents in clinical trials were headache, diarrhoea, nausea, and rash, which were generally of mild to moderate severity. Approximately 1% of patients discontinued participation in the clinical studies due to these events. All adverse events were reported with similar frequency in EMTRIVA and control treatment groups with the exception of skin discoloration which was reported with higher frequency in the EMTRIVA treated group.

Skin discoloration, manifested by hyperpigmentation on the palms and/or soles was generally mild and asymptomatic. The mechanism and clinical significance are unknown.

In addition to the adverse reactions reported in adults, anaemia has been reported commonly and hyperpigmentation very commonly, in paediatric patients.

Efavirenz: Efavirenz was generally well tolerated in clinical trials. Efavirenz has been studied in over 9,000 patients. In a subset of 1,008 patients who received efavirenz 600 mg daily in combination with PIs and/or NRTIs in controlled clinical studies, the most frequently reported undesirable effects of at least moderate severity reported in at least 5% of patients were rash (11.6%), dizziness (8.5%), nausea (8.0%), headache (5.7%) and fatigue (5.5%). The most significant adverse events observed in patients treated with efavirenz are nervous system symptoms (see PRECAUTIONS, Nervous System Symptoms), psychiatric symptoms (see PRECAUTIONS, Psychiatric Symptoms), and rash (see PRECAUTIONS, Skin Rash).

Other, less frequent, clinically significant treatment related undesirable effects reported in all clinical trials include: allergic reaction, abnormal coordination, ataxia, confusion, stupor, vertigo, vomiting, diarrhoea, hepatitis, impaired concentration, insomnia, anxiety, abnormal dreams, somnolence, depression, abnormal thinking, agitation, amnesia, delirium, emotional lability, euphoria, hallucination and psychosis.

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

CLINICAL TRIALS

Tenofovir disoproxil fumarate + Emtricitabine + Efavirenz:

Study 934: Study 934 was an open-label active-controlled study in which 511 antiretroviral-naïve patients received either tenofovir DF, emtricitabine and efavirenz in combination (n=257) or Combivir (lamivudine/zidovudine) administered in combination with efavirenz (n=254). Adverse events observed in this study were generally consistent with those seen in previous studies in treatment-experienced or treatment-naïve patients (Table 5). Adverse events leading to study drug discontinuation occurred in significantly smaller number of patients in the TRUVADA group compared to the Combivir group (5% vs 11%, p=0.010). The most frequently occurring adverse event leading to study drug discontinuation was anaemia (including decreased haemoglobin), no patient in the TRUVADA group and 6% of patients in the Combivir group.

Table 5. Selected Treatment-Emergent Adverse Reactions¹ (Grades 2-4) Reported in ≥5% in Any Treatment Group in Study 934 (0-144 weeks)

	TRUVADA ² + EFV N=257	Combivir+EFV N=254
Gastrointestinal Disorders		
Diarrhoea	9%	5%
Nausea	9%	7%
Vomiting	2%	5%
General Disorders and Administration Site Condition		
Fatigue	9%	8%
Infections and Infestations		
Sinusitis	8%	4%
Upper Respiratory Tract Infections	8%	5%
Nasopharyngitis	5%	3%
Nervous System Disorders		
Headache	6%	5%
Dizziness	8%	7%
Psychiatric Disorders		
Depression	9%	7%
Insomnia	5%	7%
Skin and Subcutaneous Tissue Disorders		
Rash ³	5%	4%

1. Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.
2. Patients received EMTRIVA + VIREAD up to week 96 and switched to TRUVADA from week 96 to 144.
3. Rash event includes rash, exfoliative rash, rash generalised, rash macular, rash maculo-papular, rash pruritic and rash vesicular

Study 073:

In Study 073, patients with stable, virologic suppression on antiretroviral therapy and no history of virologic failure were randomised to receive ATRIPLA or to stay on their baseline regimen. The adverse reactions observed in Study 073 were generally consistent with those seen in Study 934 and those seen with the individual components of ATRIPLA when each was administered in combination with other antiretroviral agents.

Laboratory Abnormalities: Laboratory abnormalities observed in this study were generally consistent with those seen in previous studies (Table 6).

Table 6. Grade 3/4 Laboratory Abnormalities Reported in >1% of Patients in Either Treatment Group Study 934 (0–144 weeks)

	TRUVADA¹ + EFV N=254	Combivir+EFV N=251
Any ≥ Grade 3 Laboratory Abnormality	30%	26%
Creatine Kinase (M: >990 U/L) (F: >845 U/L)	9%	7%
Serum Amylase (>175 U/L)	8%	4%
AST (M: >180 U/L) (F: >170 U/L)	3%	3%
ALT (M: >215 U/L) (F: >170 U/L)	2%	3%
Hyperglycaemia (>250 mg/dL)	2%	1%
Haematuria (>75 RBC/HPF)	3%	2%
Neutrophil (<750/mm ³)	3%	5%
Triglyceride (>750 mg/dL)	5%	3%
Haemoglobin (<7.0 g/dL)	0%	2%

1. Patients received EMTRIVA + VIREAD up to week 96 and switched to TRUVADA from week 96 to 144.

Laboratory abnormalities observed in Study 073 were generally consistent with those in Study 934.

POST MARKETING SURVEILLANCE

In addition to adverse events reported from clinical trials, the following events have been reported in post marketing surveillance. Because these events have been reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Tenofovir disoproxil fumarate

IMMUNE SYSTEM DISORDERS

Allergic reaction (including angioedema)

METABOLISM AND NUTRITION DISORDERS

Hypokalaemia, hypophosphataemia, lactic acidosis

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS

Dyspnoea

GASTROINTESTINAL DISORDERS

Increased amylase, abdominal pain, pancreatitis

HEPATOBIILIARY DISORDERS

Hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT, gamma GT)

SKIN AND SUBCUTANEOUS TISSUE DISORDERS

Rash

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS

Rhabdomyolysis, muscular weakness, myopathy, osteomalacia (manifested as bone pain and infrequently contributing to fractures)

RENAL AND URINARY DISORDERS

Increased creatinine, renal insufficiency, renal failure, acute renal failure, Fanconi syndrome, proximal renal tubulopathy, nephrogenic diabetes insipidus, proteinuria, acute tubular necrosis, polyuria, interstitial nephritis (including acute cases).

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS

Asthaenia

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), hypokalaemia, muscular weakness, myopathy, hypophosphataemia. These events are not considered to be causally associated with tenofovir DF therapy in the absence of proximal renal tubulopathy.

Immune Reconstitution Syndrome: In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy, an inflammatory reaction to infectious pathogens (active or inactive) may arise (see PRECAUTIONS).

Exacerbations of Hepatitis after Discontinuation of Treatment: In HIV infected patients co-infected with HBV, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of treatment (see PRECAUTIONS).

Emtricitabine

Immune Reconstitution Syndrome: In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy, an inflammatory reaction to infectious pathogens (active or inactive) may arise (see PRECAUTIONS).

Efavirenz

PSYCHIATRIC DISORDERS

Completed suicide, psychosis, delusion, neurosis

NERVOUS SYSTEM DISORDERS

Convulsions, cerebellar coordination and balance disturbances, tremor

EYE DISORDERS

Blurred vision

EAR AND LABYRINTH DISORDERS

Tinnitus

GASTROINTESTINAL DISORDERS

Abdominal pain, pancreatitis

HEPATOBIILIARY DISORDERS

Hepatic failure

SKIN AND SUBCUTANEOUS TISSUE DISORDERS

Pruritus, photoallergic dermatitis

VASCULAR DISORDERS

Flushing

REPRODUCTIVE SYSTEM AND BREAST DISORDERS

Gyneecomastia

A few of the post marketing reports of hepatic failure, including cases in patients with no pre-existing hepatic disease or other identifiable risk factors, were characterized by a fulminant course, progressing in some cases to transplantation or death.

Immune Reconstitution Syndrome: In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy, an inflammatory reaction to infectious pathogens (active or inactive) may arise (see PRECAUTIONS).

Use in Children

ATRIPLA is not recommended for use in children below 18 years of age due to insufficient data on safety and efficacy.

Undesirable effects with an altered frequency have been observed in paediatric patients following the administration of efavirenz or emtricitabine.

Undesirable effects in children receiving efavirenz were generally similar to those of adult patients; however, rash was reported more frequently in children and was more often of higher grade than in adults. Rash was reported in 26 of 57 children (46%) treated with efavirenz.

In addition to the adverse reactions reported in adults, anaemia was common and hyperpigmentation was very common in paediatric patients receiving emtricitabine in a clinical study.

DOSAGE AND ADMINISTRATION

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

Children and adolescents: ATRIPLA is not recommended for use in children below 18 years of age due to insufficient data on safety and efficacy.

Elderly: ATRIPLA should be administered with caution to elderly patients (see PRECAUTIONS).

Renal impairment: ATRIPLA is not recommended for patients with moderate or severe renal impairment (Creatinine Clearance (CrCl) < 50 mL/min). Patients with moderate or severe renal impairment require dose interval adjustments of tenofovir DF and emtricitabine that cannot be achieved with the combination tablet (see PRECAUTIONS).

The safety and efficacy of once daily dosing of tenofovir DF with emtricitabine in patients with mild renal impairment (CrCl 50 to 80 mL/min), have been demonstrated in clinical studies. No dosage adjustment is recommended for patients with renal impairment who receive efavirenz. Therefore no dosage adjustment is required for ATRIPLA in patients with mild renal impairment.

Hepatic impairment: The pharmacokinetics of ATRIPLA have not been studied in patients with hepatic impairment. Caution should be exercised in administering ATRIPLA to patients with liver disease due to the efavirenz component (see PRECAUTIONS).

Where discontinuation of ATRIPLA is necessary due to one of the components, or where dose modification is necessary, separate preparations of tenofovir DF, emtricitabine and efavirenz are available. Please refer to the product information for these products.

OVERDOSAGE

Treatment of overdose with ATRIPLA should consist of general supportive measures, including monitoring of vital signs and observation of the patient's clinical status. Administration of activated charcoal may be used to aid removal of unabsorbed efavirenz. There is no specific antidote for overdose with efavirenz. Haemodialysis can remove both tenofovir DF and emtricitabine (refer to detailed information below). However, since efavirenz is highly protein bound, dialysis is unlikely to remove significant quantities of it from blood.

Tenofovir disoproxil fumarate: Tenofovir can be removed by haemodialysis; the median haemodialysis clearance of tenofovir is 134 mL/min. The elimination of tenofovir by peritoneal dialysis has not been studied.

Emtricitabine: Emtricitabine can be removed by haemodialysis, which removes approximately 30% of the emtricitabine dose over a 3-hour dialysis period starting within 1.5 hours of emtricitabine dosing. It is not known whether emtricitabine can be removed by peritoneal dialysis.

Efavirenz: Some patients accidentally taking 600 mg twice daily have reported increased nervous system symptoms. One patient experienced involuntary muscle contractions.

PRESENTATION AND STORAGE CONDITIONS

ATRIPLA is available as tablets. Each tablet contains 300 mg tenofovir DF (which is equivalent to 245 mg of tenofovir disoproxil), 200 mg emtricitabine and 600 mg efavirenz. The tablets are capsule shaped and pink in colour. Each tablet is debossed with '123' on one side and plain on the other side.

ATRIPLA is supplied in high density polyethylene (HDPE) bottles containing 30 tablets and a desiccant (silica gel canister or sachet) and is closed with a screw cap closure.

ATRIPLA should be stored below 30 °C.

MEDICINES CLASSIFICATION

Prescription Medicine

NAME AND ADDRESS OF SPONSOR

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Auckland

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