SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

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

Tablets

COMPOSITION

Each tablet contains 600 mg of efavirenz, 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate (DF) (which is equivalent to 245 mg of tenofovir disoproxil) as active ingredients. The tablets include the following inactive ingredients: Croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose and sodium lauryl sulphate. The tablets are film-coated with a coating material containing polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

ATRIPLA tablets contain no sugar.

PHARMACOLOGICAL CLASSIFICATION

A.20.2.8 Antiviral agents

PHARMACOLOGICAL ACTION

Pharmacodynamics

ATRIPLA is a fixed dose combination tablet containing efavirenz, emtricitabine and tenofovir disoproxil fumarate (tenofovir DF). Efavirenz is a non-nucleoside reverse transcriptase inhibitor; emtricitabine is a synthetic nucleoside analogue of cytidine, and tenofovir DF is converted *in vivo* to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analogue of adenosine 5′-monophosphate.

Mechanism of Action

Efavirenz: Efavirenz is a non-nucleoside reverse transcriptase inhibitor of HIV-1. Efavirenz activity is mediated predominantly by non-competitive inhibition of HIV-1 reverse transcriptase (RT). HIV-2 RT and human cellular DNA polymerases α, β, γ and δ are not inhibited by efavirenz.

Emtricitabine: Emtricitabine, a synthetic nucleoside analogue 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 and by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine 5′-triphosphate is a weak inhibitor of mammalian DNA polymerase α, β, ε and mitochondrial DNA polymerase γ.

Tenofovir disoproxil fumarate: Tenofovir DF is an acyclic nucleoside phosphonate diester analogue 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 HIV-1 RT by competing with the natural substrate deoxyadenosine 5′-triphosphate and after incorporation into DNA, by DNA

chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β and mitochondrial DNA polymerase γ.

Antiviral Activity

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

Efavirenz: The concentration of efavirenz inhibiting replication of wild-type laboratory adapted strains and clinical isolates in cell culture by 90 to 95 % (EC_{90-95}) ranged from 1,7 to 25 nM in lymphoblastoid cell lines, peripheral blood mononuclear cells and macrophage/monocyte cultures. Efavirenz demonstrated additive antiviral activity against HIV-1 in cell culture when combined with non-nucleoside reverse transcriptase inhibitors (NNRTIs) (delavirdine and nevirapine), nucleoside reverse transcriptase inhibitors (NRTIs) (abacavir, didanosine, lamivudine, stavudine, zalcitabine and zidovudine), protease inhibitors (PIs) (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir and saquinavir) and the fusion inhibitor enfuvirtide. Efavirenz demonstrated additive to antagonistic antiviral activity in cell culture with atazanavir. Efavirenz demonstrated antiviral activity against most non-clade B isolates (subtypes A, AE, AG, C, D, F, G, J and N), but had reduced antiviral activity against group O viruses. Efavirenz is not active against HIV-2.

Emtricitabine: The antiviral activity in cell culture 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 50 % effective concentration (EC_{50}) values for

emtricitabine were in the range of 0,0013 to 0,64 μM (0,0003 to 0,158 μg/ml). In medicine combination studies of emtricitabine with NRTIs (abacavir, lamivudine, stavudine, zalcitabine and zidovudine), NNRTIs (delavirdine, efavirenz and nevirapine), and PIs (amprenavir, nelfinavir, ritonavir and saquinavir), additive to synergistic effects were observed. Emtricitabine displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F and G (EC_{50} values ranged from 0,007 to 0,075 μM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 0,007 to 1,5 μM).

Tenofovir disoproxil fumarate: The antiviral activity in cell culture 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 EC_{50} values for tenofovir were in the range of 0,04 to 8,5 μM. In medicine combination studies of tenofovir with NRTIs (abacavir, didanosine, lamivudine, stavudine, zalcitabine and zidovudine), NNRTIs (delavirdine, efavirenz and nevirapine), and PIs (amprenavir, indinavir, nelfinavir, ritonavir and saquinavir), additive to synergistic effects were observed. Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G and O (EC_{50} values ranged from 0,5 to 2,2 μM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 1,6 μM to 4,9 μM).

Medicine Resistance

Efavirenz, emtricitabine, and tenofovir disoproxil fumarate: HIV-1 isolates with reduced susceptibility to the combination of emtricitabine and tenofovir have been selected in cell culture and in clinical studies. Genotypic analysis of these isolates identified the M184V/I and/or K65R amino acid substitutions in the viral RT. In a clinical study of treatment-naïve patients (Study 934, see **INDICATIONS** and **DOSAGE AND DIRECTIONS FOR USE**) resistance analysis was performed on HIV isolates from all virologic failure patients with > 400 copies/ml of HIV-1 RNA

at Week 48 or early discontinuations. Genotypic resistance to efavirenz, predominantly the K103N substitution, was the most common form of resistance that developed. Resistance to efavirenz occurred in 9/12 (75 %) analysed patients in the emtricitabine + tenofovir DF group and in 16/22 (73 %) analysed patients in the zidovudine/lamivudine fixed-dose combination group. The M184V amino acid substitution, associated with resistance to emtricitabine and lamivudine, was observed in 2/12 (17 %) analysed patient isolates in the emtricitabine + tenofovir DF group and in 7/22 (32 %) analysed patient isolates in the zidovudine/lamivudine group. Through 48 weeks of Study 934, no patients developed a detectable K65R mutation in their HIV as analysed through standard genotypic analysis. Insufficient data are available to assess the development of the K65R mutation upon prolonged exposure to this regimen.

In a clinical study of treatment-naïve patients, isolates from 8 of 47 patients receiving tenofovir DF developed the K65R substitution through 144 weeks of therapy; 7 of these occurred in the first 48 weeks of treatment and 1 at Week 96. In treatment experienced patients, 14/304 (5 %) of tenofovir DF treated patients with virologic failure through Week 96 showed > 1,4 fold (median 2,7) reduced susceptibility to tenofovir. Genotypic analysis of the resistant isolates showed a mutation in the HIV-1 RT gene resulting in the K65R amino acid substitution.

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

HIV-1 isolates with reduced susceptibility to efavirenz (> 380-fold increase in EC_{90} value) emerged rapidly under selection in cell culture. Genotypic characterisation of these viruses identified mutations resulting in single amino acid substitutions L100I or V179D, double substitutions L100I/V108I and triple substitutions L100I/V179D/Y181C in RT.

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

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

Cross-Resistance

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

Efavirenz: Clinical isolates previously characterised as efavirenz-resistant were also phenotypically resistant in cell culture to delavirdine and nevirapine compared to baseline. Delavirdine- and/or nevirapine-resistant clinical viral isolates with NNRTI resistance-associated

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

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

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

Pharmacokinetics

ATRIPLA: One ATRIPLA tablet is bioequivalent to one 600 mg efavirenz + 200 mg emtricitabine + 300 mg tenofovir DF following single-dose administration to fasting healthy subjects (N=45).

Efavirenz: In HIV-infected patients time-to-peak plasma concentrations were approximately 3 to 5 hours and steady-state plasma concentrations were reached in 6 to 10 days. In 35 patients receiving efavirenz 600 mg once daily, steady-state C_{max} was 12,9 ± 3,7 μM (mean ± SD), C_{min} was 5,6 ± 3,2 μM, and AUC was 184 ± 73 μM·hr. Efavirenz is highly bound (approximately 99,5 to 99,75 %) to human plasma proteins, predominantly albumin. Following administration of ^{14}C-labelled efavirenz, 14 to 34 % of the dose was recovered in the urine (mostly as metabolites) and 16 to 61 % was recovered in faeces (mostly as parent medicine). *In vitro* studies suggest CYP3A4 and CYP2B6 are the major isozymes responsible for efavirenz metabolism. Efavirenz has been shown to induce P450 enzymes, resulting in induction of its own metabolism. Efavirenz has a terminal half-life of 52 to 76 hours after single doses and 40 to 55 hours after multiple doses.

Emtricitabine: Following oral administration, emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1 to 2 hours post-dose. Following multiple dose oral administration of emtricitabine to 20 HIV-infected subjects, the steady-state plasma emtricitabine C_{max} was 1,8 ± 0,7 μg/ml (mean ± SD) and the AUC over a 24-hour dosing interval was 10,0 ± 3,1 μg•hr/ml. The mean steady state plasma trough concentration at 24 hours post-dose was 0,09 μg/ml. The mean absolute bioavailability of emtricitabine was 93 %. *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 radio-labelled 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 with a renal

clearance in adults with normal renal function of 213 ± 89 ml/min (mean ± SD). Following a single oral dose, the plasma emtricitabine half-life is approximately 10 hours.

Tenofovir disoproxil fumarate: Following oral administration of a single 300 mg dose of tenofovir DF to HIV-1 infected patients in the fasted state, maximum serum concentrations (C_{max}) were achieved in 1,0 ± 0,4 hours (mean ± SD) and C_{max} and AUC values were 296 ± 90 ng/ml and 2 287 ± 685 ng•hr/ml, respectively. The oral bioavailability of tenofovir from tenofovir DF in fasted patients is approximately 25 %. *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 medicine in the urine. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion with a renal clearance in adults with normal renal function of 243 ± 33 ml/min (mean ± SD). Following a single oral dose, the terminal elimination half-life of tenofovir is approximately 17 hours.

Effects of Food on Oral Absorption

ATRIPLA has not been evaluated in the presence of food. Administration of efavirenz tablets with a high fat 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 (see **KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENTS** and **SIDE EFFECTS, WARNINGS AND SPECIAL PRECAUTIONS**).

Special Populations

Race

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

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

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

Gender

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

Paediatric and Geriatric Patients

Pharmacokinetic studies of tenofovir DF have not been performed in paediatric patients (< 18 years). Efavirenz has not been studied in paediatric patients below 3 years of age or who weigh < 13 kg. Emtricitabine has been studied in paediatric patients from 3 months to 17 years of age. ATRIPLA is not recommended for paediatric administration. Pharmacokinetics of efavirenz, emtricitabine and tenofovir have not been fully evaluated in the elderly (> 65 years) (see **SIDE EFFECTS** and **WARNINGS AND SPECIAL PRECAUTIONS**).

Patients with Impaired Renal Function

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

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

Patients with Hepatic Impairment

Efavirenz: The pharmacokinetics of efavirenz have not been adequately studied in patients with hepatic impairment (see **SIDE EFFECTS** and **WARNINGS AND SPECIAL PRECAUTIONS**).

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

Tenofovir disoproxil fumarate: 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.

Pregnancy (see **WARNINGS AND SPECIAL PRECAUTIONS** and **PREGNANCY AND LACTATION, Pregnancy**)

Nursing Mothers (see **PREGNANCY AND LACTATION, Lactation**)

Summary of Clinical Studies

Clinical Study 934 supports the use of ATRIPLA Tablets in antiretroviral treatment-naïve HIV-1 infected patients. Additional data in support of the use of ATRIPLA in treatment-naïve patients can be found in the package insert for VIREAD.

In antiretroviral treatment-experienced patients, the use of ATRIPLA Tablets may be considered for patients with HIV strains that are expected to be susceptible to the components of ATRIPLA as assessed by treatment history or by genotypic or phenotypic testing (see **PHARMACOLOGICAL ACTION, Pharmacodynamics, Medicine Resistance** and **Cross Resistance**).

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

Data through 48 weeks are reported for Study 934, a randomised, open-label, active-controlled multi-centre study comparing emtricitabine + tenofovir DF administered in combination with efavirenz versus zidovudine/lamivudine fixed-dose combination administered in combination with efavirenz in 511 antiretroviral-naïve patients. 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/mm^3 (range 2 to 1 191) and median baseline plasma HIV-1 RNA was 5,01 log_{10} copies/ml (range 3,56 to 6,54). Patients were stratified by baseline CD4 count (< or ≥ 200 cells/mm^3) and 41 % had CD4 cell counts < 200 cells/mm^3. Fifty-one percent (51 %) of patients had baseline viral loads > 100 000 copies/ml. Treatment outcomes through 48 weeks for those patients who did not have efavirenz resistance at baseline (N=487) are presented in **Table 1**.

Table 1

Outcomes of Randomised Treatment at Week 48 (Study 934)

Outcome at Week 48	**FTC + TDF + EFV (N=244)**	**AZT/3TC + EFV (N=243)**

	%	%
Responder[1]	84 %	73 %
Virologic failure[2]	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[3]	10 %	14 %

[1.] Patients achieved and maintained confirmed HIV-1 RNA < 400 copies/ml through Week 48.

[2.] Includes confirmed viral rebound and failure to achieve confirmed < 400 copies/ml through Week 48.

[3.] Includes lost to follow-up, patient withdrawal, non-compliance, protocol violation and other reasons.

The difference in the proportion of patients who achieved and maintained HIV-1 RNA < 400 copies/ml through 48 weeks largely results from the higher number of discontinuations due to adverse events and other reasons in the zidovudine/lamivudine group in this open-label study. In addition, 80 % and 70 % of patients in the emtricitabine + tenofovir DF and the zidovudine/lamivudine group, respectively, achieved and maintained HIV-1 RNA < 50 copies/ml. The mean increase from baseline in CD4 cell count was 190 cells/mm^3 in the emtricitabine + tenofovir DF group and 158 cells/mm^3 for the zidovudine/lamivudine group.

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

INDICATIONS

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

CONTRAINDICATIONS

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

ATRIPLA should not be administered concurrently with astemizole, bepridil, cisapride, midazolam, pimozide, triazolam or ergot derivatives because competition for CYP3A4 by efavirenz could result in inhibition of metabolism of these medicines and create the potential for serious and/or life-threatening adverse events (e.g. cardiac arrhythmias, prolonged sedation or respiratory depression). ATRIPLA should not be administered concurrently with voriconazole because efavirenz significantly decreases voriconazole plasma concentrations (see **INTERACTIONS**).

ATRIPLA is contraindicated in patients with moderate to severe renal impairment [Creatinine Clearance < 50 ml/min (see **WARNINGS AND SPECIAL PRECAUTIONS** and **PHARMACOLOGICAL ACTION, Pharmacokinetics**)].

WARNINGS AND SPECIAL PRECAUTIONS

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.

ATRIPLA IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION AND THE SAFETY AND EFFICACY OF ATRIPLA HAVE NOT BEEN ESTABLISHED IN PATIENTS CO-INFECTED WITH HBV AND HIV. SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO HAVE DISCONTINUED EMTRICITABINE OR TENOFOVIR, 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 CO-INFECTED WITH HIV AND HBV AND DISCONTINUE ATRIPLA. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (see **WARNINGS AND SPECIAL PRECAUTIONS**).

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination with other antiretrovirals. 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).

Routine testing of serum lactate levels in asymptomatic patients on ART is not recommended. Measurement of serum lactate levels is recommended only for patients presenting with clinical signs or symptoms consistent with lactic acidosis.

Lactate 2 to 5 mmol/l: Monitor regularly, and be alert for clinical signs.

Lactate 5 to 10 mmol/l without symptoms: Monitor closely.

Lactate 5 to 10 mmol/l with symptoms: STOP all therapy. Exclude other causes (e.g. sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis, lymphoma).

Lactate ≥ 10 mmol/l: STOP all therapy (80 % mortality in case studies).

Patients Co-infected with HIV and HBV

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

Co-administration with Related Medicines

Related medicines not for co-administration with ATRIPLA include emtricitabine, tenofovir DF, emtricitabine/tenofovir DF and efavirenz, which contain the same active components as

ATRIPLA. Due to similarities between emtricitabine and lamivudine, ATRIPLA should not be co-administered with medicines containing lamivudine, including lamivudine/zidovudine, lamivudine, abacavir sulphate/lamivudine or abacavir sulphate/lamivudine/zidovudine.

Medicine Interactions (see INTERACTIONS)

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

Psychiatric Symptoms

Serious psychiatric adverse experiences have been reported in patients treated with efavirenz. In controlled trials of 1 008 patients treated with regimens containing efavirenz for a mean of 2,1 years and 635 patients treated with control regimens for a mean of 1,5 years, the frequency of specific serious psychiatric events among patients who received efavirenz or control regimens, respectively, were: Severe depression (2,4 %, 0,9 %), suicidal ideation (0,7 %, 0,3 %), non-fatal suicide attempts (0,5 %, 0 %), aggressive behaviour (0,4 %, 0,5 %), paranoid reactions (0,4 %, 0,3 %) and manic reactions (0,2 %, 0,3 %). When psychiatric symptoms similar to those noted above were combined and evaluated as a group in a multifactorial analysis of data from Study AI266006 (006), treatment with efavirenz was associated with an increase in the occurrence of these selected psychiatric symptoms. Other factors associated with an increase in the occurrence of these psychiatric symptoms were history of injection medicine use, psychiatric history and receipt of psychiatric medication at study entry; similar associations were observed in both the efavirenz and control treatment groups. In Study 006, onset of new serious psychiatric symptoms occurred throughout the study for both efavirenz-treated and control-

treated patients. One percent of efavirenz-treated patients discontinued or interrupted treatment because of one or more of these selected psychiatric symptoms. There have also been occasional post-marketing 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 with serious psychiatric adverse experiences should seek immediate medical evaluation to assess the possibility that the symptoms may be related to the use of efavirenz, and if so, to determine whether the risks of continued therapy outweigh the benefits (see **SIDE EFFECTS**).

Nervous System Symptoms

Fifty-three percent of patients receiving efavirenz in controlled trials reported central nervous system symptoms compared to 25 % of patients receiving control regimens. These symptoms included dizziness (28,1 %), insomnia (16,3 %), impaired concentration (8,3 %), somnolence (7,0 %), abnormal dreams (6,2 %) and hallucinations (1,2 %). Other reported symptoms were euphoria, confusion, agitation, amnesia, stupor, abnormal thinking and depersonalisation. The majority of these symptoms were mild-moderate (50,7 %); symptoms were severe in 2,0 % of patients. Overall, 2,1 % of patients discontinued therapy as a result. These symptoms usually begin during the first or second day of therapy and generally resolve after the first 2 to 4 weeks of therapy. After 4 weeks of therapy, the prevalence of nervous system symptoms of at least moderate severity ranged from 5 % to 9 % in patients treated with regimens containing efavirenz and from 3 % to 5 % in patients treated with a control regimen. Patients should be informed that these common symptoms were likely to improve with continued therapy and were not predictive of subsequent onset of the less frequent psychiatric symptoms (see **WARNINGS AND SPECIAL PRECAUTIONS, Psychiatric Symptoms**). Dosing at bedtime may improve the tolerability of these nervous system symptoms (see **SIDE EFFECTS** and **DOSAGE AND DIRECTIONS FOR USE**).

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

Patients receiving ATRIPLA should be alerted to the potential for additive central nervous system effects when ATRIPLA is used concomitantly with alcohol or psycho-active medicines.

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

Renal Impairment (see CONTRAINDICATIONS)

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

$$\text{CrCl (ml/min)} = \frac{140 - \text{age (years)} \times \text{weight (kg)} \; [\times 0{,}85 \text{ if female}]}{72 \times \text{serum creatinine (mg/dl)}}$$

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphataemia), has been reported in association with the use of tenofovir DF (see **SIDE EFFECTS, Post-Marketing Experience**).

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

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

Reproductive Risk Potential

Efavirenz may cause foetal harm when administered during the first trimester to a pregnant woman. Pregnancy should be avoided in women receiving ATRIPLA. Barrier contraception should 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 this medicine is used during the first trimester of pregnancy, or if the patient becomes pregnant while taking this medicine, the patient should be apprised of the potential harm to the foetus.

There are no adequate and well-controlled studies of ATRIPLA in pregnant women.

Efavirenz: As of July 2006, the antiretroviral Pregnancy Registry has received prospective reports of 322 pregnancies exposed to efavirenz-containing regimens, nearly all of which were first-trimester exposures (316 pregnancies). Birth defects occurred in 6 of 255 live births (first-trimester exposure) and 1 of 17 live births (second/third-trimester exposure). None of these prospectively reported defects were neural tube defects. However, there have been four retrospective reports of findings consistent with neural tube defects, including meningomyelocele. All mothers were exposed to efavirenz-containing regimens in the first

trimester. Although a causal relationship of these events to the use of efavirenz has not been established, similar defects have been observed in pre-clinical studies of efavirenz.

Paediatric Use

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

Geriatric Use

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

Skin Rash

In controlled clinical trials, 26 % (266/1 008) of patients treated with 600 mg efavirenz experienced new-onset skin rash compared with 17 % (111/635) of patients treated in control groups. Rash associated with blistering, moist desquamation or ulceration occurred in 0,9 % (9/1 008) of patients treated with efavirenz. The incidence of Grade 4 rash (e.g. erythema multiforme, Stevens-Johnson syndrome) in patients treated with efavirenz in all studies and expanded access was 0,1 %. Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first 2 weeks of initiating therapy with efavirenz (median time to onset of rash in adults was 11 days) and, in most patients continuing therapy with efavirenz, rash resolves within 1 month (median duration, 16 days). The discontinuation rate for rash in clinical trials was 1,7 % (17/1 008). ATRIPLA can be reinitiated in patients interrupting therapy

because of rash. ATRIPLA should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash.

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

Liver Enzymes

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 (see **WARNINGS AND SPECIAL PRECAUTIONS, Patients Co-infected with HIV and HBV**). In patients with persistent elevations of serum transaminases to > 5 X 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 **SIDE EFFECTS, Laboratory Abnormalities**).

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

Bone Effects

In a 144-week study of treatment naïve patients, decreases in bone mineral density (BMD) were seen at the lumbar spine and hip in both arms of the study. At Week 144, there was a

significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in patients receiving tenofovir DF + lamivudine + efavirenz compared with patients receiving stavudine + lamivudine + efavirenz. Changes in BMD at the hip were similar between the two treatment groups. In both groups, the majority of the reduction in BMD occurred in the first 24 to 48 weeks of the study and this reduction was sustained through 144 weeks. Twenty-eight percent of tenofovir DF treated patients versus 21 % of the comparator patients lost at least 5 % of BMD at the spine or 7 % of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 patients in the tenofovir DF group and 6 patients in the comparator group. Tenofovir DF was associated with significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide and urinary N-telopeptide), suggesting increased bone turnover. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in patients receiving tenofovir DF. The effects of tenofovir DF associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. For additional information, please consult the tenofovir DF package insert.

Cases of osteomalacia (associated with proximal renal tubulopathy) have been reported in association with the use of tenofovir DF (see **SIDE EFFECTS, Post-Marketing Experience**).

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

Convulsions

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

Patients who are receiving concomitant anticonvulsant medications primarily metabolised by the liver, such as phenytoin and phenobarbital, may require periodic monitoring of plasma levels (see **INTERACTIONS**).

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

Fat Redistribution

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

Immune Reconstitution Syndrome

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

INTERACTIONS (see also CONTRAINDICATIONS and WARNINGS AND SPECIAL PRECAUTIONS)

Efavirenz: Efavirenz has been shown *in vivo* to induce CYP3A4. Other compounds that are substrates of CYP3A4 may have decreased plasma concentrations when co-administered with efavirenz. *In vitro* studies have demonstrated that efavirenz inhibits 2C9, 2C19 and 3A4 isozymes in the range of observed efavirenz plasma concentrations. Co-administration of efavirenz with medicines primarily metabolised by these isozymes may result in altered plasma concentrations of the co-administered medicine. Therefore, appropriate dose adjustments may be necessary for these medicines.

Medicines which induce CYP3A4 activity (e.g. phenobarbital, rifampin, rifabutin) would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations.

Emtricitabine and tenofovir disoproxil fumarate: Since emtricitabine and tenofovir are primarily eliminated by the kidneys, co-administration of ATRIPLA with medicines that reduce renal function or compete for active tubular secretion may increase serum concentrations of emtricitabine, tenofovir and/or other renally eliminated medicines. Some examples include, but are not limited to, acyclovir, adefovir dipivoxil, cidofovir, ganciclovir, valacyclovir and valganciclovir.

Co-administration of tenofovir DF 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 (for didanosine dosing adjustment recommendations, see **Table 3**

below in the **INTERACTIONS** section). Suppression of CD4 cell counts has been observed in patients receiving tenofovir DF with didanosine at a dose of 400 mg daily.

Atazanavir and lopinavir/ritonavir have been shown to increase tenofovir concentrations. The mechanism of this interaction is unknown. Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders. Patients receiving either atazanavir or lopinavir/ritonavir with tenofovir DF should be monitored for tenofovir-associated adverse events. ATRIPLA should be discontinued in patients who develop tenofovir-associated adverse events (for atazanavir dosing adjustment recommendations, see **Table 3** below in the **INTERACTIONS** section).

Other important medicine interaction information for ATRIPLA is summarized in **Table 2** and **3**. The medicine interactions described are based on studies conducted with efavirenz, emtricitabine or tenofovir DF as individual agents or are potential medicine interactions; no medicine interaction studies have been conducted using ATRIPLA. The tables include potentially significant interactions, but are not all inclusive.

Table 2

Medicines that are Contraindicated or not Recommended for Use with ATRIPLA

Medicine Class: Medicine Name	**Clinical Comment**
Antifungal: Voriconazole	CONTRAINDICATED because efavirenz significantly decreases voriconazole plasma concentrations and co-administration may decrease the therapeutic effectiveness of voriconazole. Also, voriconazole significantly increases efavirenz plasma

	concentrations, which may increase the risk of efavirenz-associated side effects.
Antihistamine: Astemizole	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.
Antimigraine: Ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine)	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterised by peripheral vasospasm and ischaemia of the extremities and other tissues.
Antiretrovirals: Efavirenz, emtricitabine, tenofovir DF, lamivudine	Not for use with ATRIPLA because the active ingredients emtricitabine, tenofovir DF, emtricitabine/tenofovir DF and efavirenz are components of ATRIPLA. Lamivudine is similar to emtricitabine.
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 dysrhythmias.
Gastrointestinal motility agent: Cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.
Neuroleptic: Pimozide	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.
St. John's wort (*Hypericum perforatum*)	NOT RECOMMENDED: Expected to substantially decrease plasma levels of efavirenz; has not been studied in combination with efavirenz.

Table 3

Established and Other Potentially Significant Medicine Interactions: Alteration in Dose or Regimen may be Recommended Based on Medicine Interaction Studies or Predicted Interaction

Concomitant Medicine Class: Medicine Name	**Effect**	**Clinical Comment**
Antiretroviral agents		
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 + 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 1 000 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). **Patients should be monitored for tenofovir-associated adverse events. ATRIPLA should be discontinued in patients who develop tenofovir-associated adverse events.**
Protease inhibitor: Ritonavir	↑ ritonavir concentration ↑ efavirenz	When ritonavir 500 mg every 12 hours was co-administered with efavirenz 600 mg once daily, the combination was associated with a higher

	concentration	frequency of adverse clinical experiences (e.g. dizziness, nausea, paraesthesia) 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.
NRTI: Didanosine	↑ didanosine concentration	Higher didanosine concentrations could potentiate didanosine-associated adverse events, including pancreatitis and neuropathy. **In adults weighing > 60 kg, the didanosine dose should be reduced to 250 mg if co-administered with ATRIPLA**. **Data are not available to recommend a dose adjustment of didanosine for patients weighing < 60 kg.** When co-administered, ATRIPLA and didanosine may be taken under fasted conditions or with a light meal (< 400 kcal, 20 % fat). Co-administration of didanosine buffered formulation with ATRIPLA should be under fasted conditions. **Co-administration 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 didanosine package insert.
Other agents		
Anticoagulant: Warfarin	↑ or ↓ warfarin concentration	Plasma concentrations and effects potentially increased or decreased by efavirenz.
Anticonvulsants: Carbamazepine	↓ carbamazepine concentration ↓ efavirenz concentration	There are insufficient data to make a dose recommendation for ATRIPLA. Alternative anticonvulsant treatment should be used.
Phenytoin Phenobarbital	↓ anticonvulsant concentration ↓ efavirenz concentration	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.
Antifungals: Itraconazole Ketoconazole	↓ itraconazole concentration ↓ hydroxy-itraconazole concentration ↓ ketoconazole concentration	Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered. Medicine interaction studies with ATRIPLA and ketoconazole have not been conducted. Efavirenz has the potential to decrease plasma

		concentrations of ketoconazole.
Anti-infective: Clarithromycin	↓ clarithromycin concentration ↑ 14-OH metabolite concentration	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.
Antimycobacterial: Rifabutin	↓ rifabutin concentration	Increase daily dose of rifabutin by 50 %. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week.
Antimycobacterial: Rifampicin	↓ efavirenz concentration	Clinical significance of reduced efavirenz concentration is unknown. Dosing recommendations for concomitant use of ATRIPLA and rifampicin have not been established.
Calcium channel blockers: Diltiazem Others (e.g. felodipine,	↓ diltiazem concentration ↓ desacetyl diltiazem concentration ↓ N-monodes-	Diltiazem dose adjustments should be guided by clinical response (refer to the complete package insert for diltiazem). No dose adjustment of ATRIPLA is necessary when administered with diltiazem. No data are available on the potential

nicardipine, nifedipine, verapamil)	methyl diltiazem concentration ↓ calcium channel blocker	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 package insert for the calcium channel blocker).
HMG-CoA reductase inhibitors: Atorvastatin Pravastatin Simvastatin	↓ atorvastatin concentration ↓ pravastatin concentration ↓ simvastatin concentration	Plasma concentrations of atorvastatin, pravastatin and simvastatin decreased with efavirenz. Consult the complete package insert for the HMG-CoA reductase inhibitor for guidance on individualising the dose.
Narcotic analgesic: Methadone	↓ methadone concentration	Co-administration of efavirenz in HIV-infected individuals with a history of injection medicine 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:	↑ ethinylestradiol	Clinical significance unknown. Because the

Ethinylestradiol	concentration	potential interaction of efavirenz with oral contraceptives has not been fully characterised, a reliable method of barrier contraception should be used in addition to oral contraceptives.

[This table is not all inclusive.]

Efavirenz Assay Interference

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

Other Interactions

Efavirenz

Medicine interaction studies were performed with efavirenz and other medicines likely to be co-administered or medicines commonly used as probes for pharmacokinetic interaction. There was no clinically significant interaction observed between efavirenz and zidovudine, lamivudine, azithromycin, fluconazole, lorazepam, cetirizine or paroxetine. Single doses of famotidine or an aluminium and magnesium antacid with simethicone had no effects on efavirenz exposures.

Emtricitabine and tenofovir disoproxil fumarate

No clinically significant medicine interactions have been observed between emtricitabine and famciclovir, indinavir, stavudine, tenofovir DF and zidovudine. Similarly, no clinically significant

medicine interactions have been observed between tenofovir DF and abacavir, adefovir dipivoxil, efavirenz, emtricitabine, indinavir, lamivudine, lopinavir/ritonavir, methadone, nelfinavir, oral contraceptives, ribavirin and saquinavir/ritonavir in studies conducted in healthy volunteers.

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

PREGNANCY AND LACTATION

Pregnancy

ATRIPLA should not be used in pregnancy.

Efavirenz may cause foetal harm when administered during the first trimester to a pregnant woman. Pregnancy should be avoided in women receiving ATRIPLA. Barrier contraception should 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 this medicine is used during the first trimester of pregnancy, or if the patient becomes pregnant while taking this medicine, the patient should be informed of the potential harm to the foetus.

There are no adequate and well-controlled studies of ATRIPLA in pregnant women.

Lactation

It is recommended that HIV-infected mothers not breastfeed their infants to avoid risking post-natal transmission of HIV. Studies in rats have demonstrated that both efavirenz and

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

DOSAGE AND DIRECTIONS FOR USE

Adults: The 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.

Paediatric: ATRIPLA is not recommended for use in patients < 18 years of age.

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

SIDE EFFECTS

For additional safety information about efavirenz, emtricitabine or tenofovir DF in combination with other antiretroviral agents, consult the package inserts for these products.

In addition to the adverse events in study 934 (**Table 4**), the following adverse events were observed in clinical studies of efavirenz, emtricitabine or tenofovir DF in combination with other antiretroviral agents.

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

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

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.

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

Skin discolouration has been reported with higher frequency among emtricitabine treated patients. Skin discolouration, manifested by hyper-pigmentation on the palms and/or soles was generally mild and asymptomatic. The mechanism and clinical significance are unknown.

In addition to the laboratory abnormalities described for Study 934 (**Table 5**), Grade 3/4 elevations of bilirubin (> 2,5 x ULN), pancreatic amylase (> 2,0 x ULN), serum glucose (< 40 or > 250 mg/dl), serum lipase (> 2,0 x ULN) and urine glucose (≥ 3+) occurred in up to 3 % of patients treated with emtricitabine or tenofovir DF with other antiretroviral agents in clinical trials.

Clinical Trials

Study 934 - Treatment Emergent Adverse Events: Study 934 was an open-label active-controlled study in which 511 antiretroviral-naïve patients received either emtricitabine + tenofovir DF administered in combination with efavirenz (N=257) or zidovudine/lamivudine administered in combination with efavirenz (N=254). Adverse events observed in this study, regardless of treatment relationship, are shown in **Table 4**.

Table 4

Selected Treatment-Emergent Adverse Events (Grades 2 to 4) Reported in ≥ 3 % in Any Treatment Group in Study 934 (0 to 48 weeks)

	FTC + TDF + EFV
	(N=257)
Gastrointestinal Disorder	
Diarrhoea	7 %
Nausea	8 %
Vomiting	1 %
General Disorders and Administration Site Condition	
Fatigue	7 %
Infections and Infestations	
Sinusitis	4 %
Upper respiratory tract infections	3 %
Nasopharyngitis	3 %
Nervous System Disorders	
Somnolence	3 %
Headache	5 %
Dizziness	8 %

Psychiatric Disorders	
Depression	4 %
Insomnia	4 %
Abnormal dreams	4 %
Skin and Subcutaneous Tissue Disorders	
Rash	5 %

Laboratory Abnormalities: Laboratory abnormalities observed in this study were generally consistent with those seen in other studies (**Table 5**).

Table 5

Significant Laboratory Abnormalities Reported in ≥ 1 % in Any Treatment Group in Study 934 (0 to 48 weeks)

	FTC + TDF + EFV
	(N=257)
Any ≥ Grade 3 Laboratory Abnormality	25 %
Fasting Cholesterol (> 240 mg/dl)	15 %
Creatine Kinase (M: > 990 U/l) (F: > 845 U/l)	7 %
Serum Amylase (> 175 U/l)	7 %
Alkaline Phosphatase (> 550 U/l)	1 %
AST (M: > 180 U/l) (F: > 170 U/l)	3 %

ALT (M: > 215 U/l) (F: > 170 U/l)	2 %
Haemoglobin (< 8,0 mg/dl)	0 %
Hyperglycaemia (> 250 mg/dl)	1 %
Haematuria (> 75 RBC/HPF)	2 %
Neutrophils (< 750/mm^3)	3 %
Fasting Triglycerides (> 750 mg/dl)	4 %

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

Hepatic Events: In Study 934, 10 patients treated with efavirenz, emtricitabine and tenofovir DF and 16 patients treated with efavirenz and fixed-dose zidovudine/lamivudine were hepatitis C antibody positive. Among these HCV co-infected patients, one patient (1/10) in the efavirenz, emtricitabine and tenofovir DF arm had elevations in ALT and AST to > 5 X ULN through 48 weeks. One patient (1/16) in the fixed-dose zidovudine/lamivudine arm had elevations in ALT to > 5 X ULN through 48 weeks. Nine patients treated with efavirenz, emtricitabine and tenofovir DF and 4 patients treated with efavirenz and fixed-dose zidovudine/lamivudine were hepatitis B surface antigen positive. None of these patients had treatment-emergent elevations in ALT and AST to > 5 X ULN through 48 weeks. No HBV and/or HCV co-infected patient discontinued from

the study due to hepatobiliary disorders (see **WARNINGS AND SPECIAL PRECAUTIONS, Liver Enzymes**).

Post-Marketing Experience

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

Efavirenz

Cardiac Disorders

Palpitations

Ear and Labyrinth Disorders

Tinnitus

Endocrine Disorders

Gynaecomastia

Eye Disorders

Abnormal vision

Gastrointestinal Disorders

Constipation, malabsorption

General Disorders and Administration Site Conditions

Asthenia

Hepatobiliary Disorders

Hepatic enzyme increase, hepatic failure, hepatitis

Immune System Disorders

Allergic reactions

Metabolism and Nutrition Disorders

Redistribution/accumulation of body fat (see **WARNINGS AND SPECIAL PRECAUTIONS, Fat Redistribution**), hypercholesterolaemia, hypertriglyceridemia

Musculoskeletal and Connective Tissue Disorders

Arthralgia, myalgia, myopathy

Nervous System Disorders

Abnormal coordination, ataxia, convulsions, hypoaesthesia, paraesthesia, neuropathy, tremor

Psychiatric Disorders

Aggressive reactions, agitation, delusions, emotional lability, mania, neurosis, paranoia, psychosis, suicide

Respiratory, Thoracic and Mediastinal Disorders

Dyspnoea

Skin and Subcutaneous Tissue Disorders

Flushing, erythema multiforme, nail disorders, photo-allergic dermatitis, skin discolouration, Stevens-Johnson syndrome.

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

Tenofovir disoproxil fumarate:

Immune System Disorders

Allergic reaction

Metabolism and Nutrition Disorders

Hypophosphataemia, lactic acidosis

Respiratory, Thoracic and Mediastinal Disorders

Dyspnoea

Gastrointestinal Disorders

Abdominal pain, increased amylase, pancreatitis

Hepatobiliary Disorders

Increased liver enzymes, hepatitis

Skin and Subcutaneous Tissue Disorders

Rash

Musculoskeletal and Connective Tissue Disorders

Myopathy, osteomalacia (both associated with proximal renal tubulopathy)

Renal and Urinary Disorders

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)

General Disorders and Administration Site Conditions

Asthenia.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENTS

If overdose occurs, the patient should be monitored for evidence of toxicity, including monitoring of vital signs and observation of the patient's clinical status; standard supportive treatment should then be applied as necessary. Administration of activated charcoal may be used to aid removal of unabsorbed efavirenz. Haemodialysis can remove both emtricitabine and tenofovir DF (refer to detailed information below), but is unlikely to significantly remove efavirenz from the blood.

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

Emtricitabine: Limited clinical experience is available at doses higher than the therapeutic dose of emtricitabine. In one clinical pharmacology study single doses of emtricitabine 1 200 mg were administered to 11 patients. No severe adverse reactions were reported.

Haemodialysis treatment removes approximately 30 % of the emtricitabine dose over a 3-hour dialysis period starting within 1,5 hours of emtricitabine dosing (blood flow rate of 400 ml/min and a dialysate flow rate of 600 ml/min). It is not known whether emtricitabine can be removed by peritoneal dialysis.

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

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

IDENTIFICATION

ATRIPLA Tablets are white, capsule-shaped, film-coated tablets debossed with 123 on both sides of the tablet.

PRESENTATION

ATRIPLA Tablets are packed in 100 ml, white, high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets, a silica desiccant and a child-resistant screw cap. The bottle is packed in a carton.

STORAGE INSTRUCTIONS

ATRIPLA Tablets should be stored at or below 30 ^{o}C. The bottle should be kept tightly closed and the silica desiccant should not be removed from the bottle after opening.

Keep out of reach of children.

REGISTRATION NUMBER

42/20.2.8/0729

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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