Application for Inclusion of efavirenz, emtricitabine and tenofovir disoproxil fumarate Fixed Dose Combination Tablet On the WHO Model List of Essential Medicines

Submitted By

MERCK SHARP & DOHME Interpharma La Celle Saint Cloud, FRANCE

October 2006

Contact Person:
Dr D. DE KORTE
106, avenue Jean Moulin - BP 62
78170 La Celle Saint Cloud
FRANCE
Tel: +33130821058
Fax: +33130821090
Donald_de_korte@merck.com

Application for Inclusion of efavirenz, emtricitabine and tenofovir Disoproxil Fumarate Fixed Dose Combination Tablet (ATRIPLA™) on WHO Model List of Essential Medicines

1. Summary statement of the proposal for inclusion:

The fixed dose combination (FDC) tablet including efavirenz (EFV), emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) is proposed for inclusion in the WHO Model List of Essential Medicines in combination with other antiretroviral agents for the treatment of HIV-1 infection.

The NNRTI-based regimen of EFV with the NRTI components of FTC and TDF is now listed as a recommended regimen for initial therapy of HIV-1 infection of adults in several treatment guidelines including the 2006 WHO Treatment Guidelines for Resource-Limited Settings and the 2006 Recommendations of the International AIDS Society (IAS). This is due to demonstrated efficacy in randomized controlled studies and favourable safety profile.

This FDC provides the first complete antiretroviral therapy for administration as a single once-daily tablet for the treatment of HIV-1 infected adults. It has the potential to further improve patients' adherence to antiretroviral treatment and thereby to optimize the possibility of long-term therapeutic success by maximizing viral suppression and minimizing the emergence of HIV resistance.

In resource-poor settings, the use of this FDC can help simplify treatment and adherence, and facilitate storage and distribution.

Therefore, we propose that EFV, FTC and TDF fixed dose combination tablet be included on WHO Model List of Essential Medicines.

2. Name of the focal point in WHO supporting the application

Charlie Gilks
HIV/AIDS Department
World Health Organisation

3. Name of the organisation(s) consulted and/or supporting the application

Not Applicable

4. International Non-proprietary Name

Efavirenz
Emtricitabine
Tenofovir disoproxil fumarate

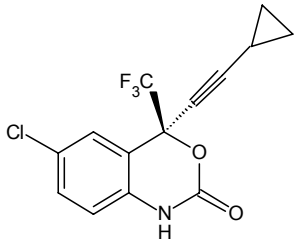
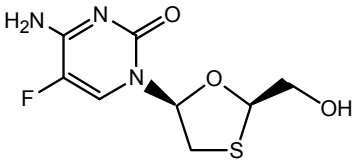
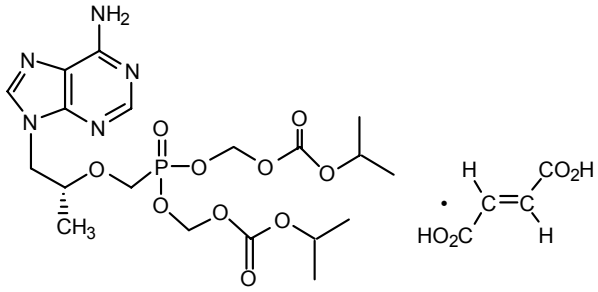
5. Formulation Proposed for Inclusion

The formulation composition of efavirenz/emtricitabine/tenofovir DF tablets is provided below:

Active Ingredients

Each tablet contains 600 mg efavirenz, 200 mg emtricitabine and 300 mg of tenofovir DF, which is equivalent to 245 mg of tenofovir disoproxil. See Table 1 below for a listing of the active ingredients of the emtricitabine and tenofovir DF fixed dose combination tablet.

Table 1: Active Ingredients of Efavirenz, Emtricitabine and Tenofovir DF Fixed Dose Combination Tablet

Approved Name	*Chemical Name, Structure al and Molecular Formulae*	*Specification or Reference*	*Qty per Tablet*
Efavirenz	(4*S*)-6-Chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2*H*-3,1-benzoxazin-2-one  $C_{14}H_9ClF_3NO_2$	In-House	600mg
Emtricitabine	5-fluoro-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine  $C_8H_{10}FN_3O_3S$	In-house	200 mg
Tenofovir disoproxil fumarate	9-[(R)-2-[[Bis[[(isopropoxycarbonyl)oxy]methoxy] phosphinyl]methoxy]propyl]adenine fumarate (1:1)  $C_{23}H_{34}N_5O_{14}P$	In-house	300 mg†

6. International Availability

Efavirenz, emtricitabine and tenofovir DF fixed dose combination tablets will be manufactured, for MSD, at any of the following facilities listed below (Table 2).

The manufacturing steps conducted at all facilities are in compliance with European Union (EU) and US FDA Good Manufacturing Practices (GMP) guidelines.

Table 2: Manufacturing Facilities for Efavirenz, Emtricitabine and Tenofovir DF Fixed Dose Combination Tablet

Commercial Manufacturing and Testing Sites	Function
Patheon, Inc. Toronto Region Operations 2100 Syntex Court Mississauga, Ontario Canada L5N 7K9	• Drug product manufacture, packaging, and labeling • Batch release testing
Patheon Inc. Burlington Century Operations 977 Century Drive Burlington, Ontario Canada L7L 5J8	• Batch release testing
Cardinal Health Germany 405 GmbH Steinbeisstrasse 2 D-73614 Schorndorf Germany	• Drug product packaging and labeling
Gilead Sciences Limited Unit 13 Stillorgan Industrial Park Blackrock Co. Dublin Ireland	• Drug Product Importer/Release into EU • Drug product packaging and labeling • Batch release testing • Batch control • Drug product release
Merck Sharp & Dohme B.V. Waarderweg 39, NL-2003 PC Haarlem The Netherlands	• Drug Product Packaging and Labeling • Batch control • Drug product release

7. Listing type requested:

Listing is requested on the Model List of Essential Medicines as an example of combination of HIV antiretrovirals in the therapeutic class of HIV nucleotide/nucleoside analogue and non nucleoside reverse transcriptase inhibitors.

8. Information supporting the public health relevance of the submission:

8.1 Epidemiological information on disease burden

Since the first clinical evidence of AIDS was reported over 25 years ago, an estimated 25 million people have died as a result of HIV infection, making it one of the most destructive epidemics in recorded history.[1] In 2005, there were an estimated 3.1 million deaths due to AIDS. Current estimates suggest that some 40.3 million people worldwide are infected with HIV, up from an estimated 37.5 million in 2003, and twice as many as compared to 1995. In 2005, it is estimated that an additional 4.9 million individuals worldwide became infected with HIV, and 700,000 of these new infections were in children <15 years of age.

Of major concern is the prevalence of HIV/AIDS in developing countries. Approximately 95% of all HIV-infected people live in low and middle-income countries.[2] Although there is new evidence that adult HIV infection rates have decreased in certain countries, the overall trends in HIV transmission are still increasing, and the overall number of people living with HIV has continued to increase in all regions of the world except the Caribbean.[3]

The steepest increases in HIV infections have occurred in Eastern Europe and Central Asia, and in East Asia. In Eastern Europe and Central Asia, there was a 25% increase in the number of people living with HIV (to 1.6 million) since 2003, and AIDS death rates almost doubled (to 62,000) during that time.[1] In East Asia there was a 20% increase in the number of people living with HIV (to 870,000) since 2003. However, the worst affected area is Sub-Saharan Africa, with 64% of new infections (3.2 million) occurring here and with an estimated 2.4 million who died of HIV-related illnesses in 2005.[1, 3]

Without HIV prevention measures, about 35% of children born to HIV-positive women will contract the virus.[1] In many countries, life expectancy and child survival rates have plummeted. For example, in seven African countries where HIV prevalence is >20%, the average life expectancy of a person born between 1995 and 2000 is now 49 years, which is 13 years lower than in the absence of AIDS.[4]

In countries already burdened by huge socio-economic challenges, HIV/AIDS threatens human social welfare, developmental progress and social stability on an unprecedented scale. HIV/AIDS continues to cripple the economic development of entire countries, because it often strikes people during their most productive period of life.[5] For example, of the 14,000 persons who became infected each day in 2005, about 12,000 (86%) were aged 15 to 49 years.[2] Overall, young people aged 15 to 24 years account for about half of all new HIV infections per day worldwide.[2]

8.2. Assessment of current use

The antiretroviral drugs do not cure the HIV infection; they only temporarily suppress viral replication and improve symptoms. They have various adverse effects and patients receiving these drugs require careful monitoring by adequately trained health professionals. For these reasons, continued rigorous promotion of measures to prevent new infections is essential and the need for this has not been diminished in any way by the addition of antiretroviral drugs. Adequate resources and trained health professionals are a prerequisite for the introduction of this class of drugs. Effective therapy requires commencement of three or four drugs simultaneously, and alternative regimens are necessary to meet specific requirements at start-up, to substitute for first-line regimens in the case of toxicity, or to replace failing regimens. The use of fixed-dose combinations can help simplify treatment, facilitate storage and

distribution, and improve patients' adherence to the treatment plan.

The introduction of potent antiretroviral agents and the combined use of these drugs have markedly reduced the replication of HIV in many patients, and improved survival rates.[6] The primary goals of antiretroviral therapy are to reduce HIV-related morbidity and mortality, improve quality of life, restore and preserve immunologic function, and maximally and durably suppress viral load.[7] Plasma viremia is a strong prognostic indicator of HIV disease progression. Reductions in plasma viremia achieved with antiretroviral therapy account for substantial clinical benefits. Therefore, suppression of plasma viremia as much as possible for as long as possible is a critical goal of antiretroviral therapy.[7]

The standardization and simplification of treatment and monitoring continues to be the prime consideration underpinning WHO recommendations for the use of ART, in order to widen access to effective therapy in resource-limited settings where individualized patient management by physicians specialized in HIV medicine is not feasible. Standardized clinical and, where available, immunological (CD4) evaluation to guide the initiation of ART, the use of appropriate formulations, including fixed-dose combinations (FDCs) of ARVs, simple laboratory tools and a symptom-directed approach to monitoring adverse events, are keys to the simplified approach.[8] WHO recommends that the first-line regimen for adults and adolescents contain two NRTIs plus one NNRTI in resource-limited settings (except for HIV-2 infections that are naturally resistant to NNRTIs), based on available evidence, clinical experience and programmatic feasibility for the wider introduction of ART.[8] The thiacytadine analogues (3TC or FTC) are pivotal to first-line regimens. 3TC or FTC should be used with a companion nucleoside or nucleotide analogue, the choices here being AZT, TDF, ABC or d4T.The preferred NRTI backbone is composed of AZT or TDF combined with either 3TC or FTC .Finally an NNRTI, either efavirenz or nevirapine should be added - both should be available for mutual substitution for toxicity and for issues related to drug choice in pregnancy and TB.[8]
Tenofovir (TDF) is now included as a preferred first-line NRTI, because of its efficacy, ease of use and safety profile. TDF has a long intracellular half life and can be used as part of once-daily regimens [8] (Table 1).

Table 1. WHO recommended first-line and second-line regimen in resource-limited settings in 2006 [8]

FIRST-LINE REGIMEN		SECOND-LINE REGIMEN	
		RTI COMPONENT	PI COMPONENT [a]
STANDARD STRATEGY	AZT or d4T + 3TC [b] + NVP or EFV	ddI + ABC or TDF + ABC or TDF + 3TC (± AZT) [c]	PI/r [d]
	TDF + 3TC [b] + + NVP or EFV	ddI + ABC or ddI + 3TC (± AZT) [c]	
	ABC + 3TC [b] + + NVP or EFV	ddI + 3TC (± AZT) [c] or TDF + 3TC (± AZT) [c]	
ALTERNATIVE STRATEGY	AZT or d4T + 3TC [b] + TDF or ABC	EFV or NVP ± ddI	

a NFV does not need refrigeration and can be used as a PI alternative in places without a cold chain.

b 3TC and FTC are considered interchangeable because they are structurally related and share pharmacological properties and resistance profiles.

c 3TC can be considered to be maintained in second-line regimens to potentially reduce viral fitness, confer residual antiviral activity and maintain pressure on the M184V mutation to improve viral sensitivity to AZT or TDF. AZT may prevent or delay the emergence of the K65R mutation.

d There are insufficient data to detect differences among currently available RTV-boosted PIs (ATV/r, FPV/r, IDV/r, LPV/r and SQV/r) and the choice should be based on individual programme priorities (see text). In the absence of a cold chain, NFV can be employed as the PI component but it is considered less potent than an RTV-boosted PI.

The NNRTI-based regimen of efavirenz with the NRTI components of emtricitabine and tenofovir is listed as a recommended regimen for initial therapy in international treatment guidelines, which include the 2006 WHO Treatment Guidelines for Resource-Limited Settings, [8] the 2005 British HIV Association Guidelines, [9] the 2004 German-Austrian Recommendations, [10] the 2005 Italian HIV treatment guidelines, [11] the 2005 Spanish HIV treatment guidelines, [12] the French 2006 HIV treatment guidelines, [13] the US Department of Health and Human Services (DHHS) 2006 Guidelines [7] **(Table 2),** and the 2006 Recommendations of the International AIDS Society – US Panel.[14]

Efavirenz 600 and the fixed dose combination of Emtricitabine / Tenofovir disoproxil fumarate are in the list of products recommended by WHO as being acceptable in principle for procurement by UN Agencies.[15]

Table 2. DHHS Antiretroviral Components Recommended for Treatment of HIV-1 Infection in Treatment Naïve Patients [7]

To Construct an Antiretroviral Regimen, Select 1 Component from Column A + 1 from Column B

	Column A		**Column B**
	NNRTI	**PI**	**2 NRTIs**
Preferred (alphabetical order)	Efavirenz	Atazanavir + ritonavir Fosamprenavir + ritonavir BID Lopinavir/ritonavir BID	Tenofovir/emtricitabine Zidovudine/lamivudine
Alternative (alphabetical order)	Nevirapine	Atazanavir (unboosted) Fosamprenavir (unboosted) Fosamprenavir + ritonavir QD Lopinavir/ritonavir QD	Abacavir/lamivudine Didanosine + lamivudine

On 12 July 2006, the US FDA granted an approval for ATRIPLA film-coated tablets, combining efavirenz, emtricitabine and tenofovir, for the treatment of HIV-1 infection in adults. This FDC provides the first complete combination antiretroviral therapy for administration as the only single, once-daily tablet for the treatment of HIV-1 infected adults. It has potential to further improve patients' adherence to the treatment regimen and thereby optimize the possibility of long-term therapeutic success by maximizing viral suppression and minimizing the emergence of HIV resistance. The FDC, which is the result of the collaboration with several pharmaceutical companies, has been welcome by several HIV experts. [16, 17]

8.3. Target population

The FDC 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.[18] Because it contains efavirenz, an NNRTI, the FDC is not indicated for the treatment of HIV-2 infection. [8]

Because efavirenz may cause fetal harm when administered during the first trimester to a pregnant woman, pregnancy should be avoided in women receiving the FDC. 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 the FDC. If the FDC is used during the first trimester of pregnancy, or if the patient becomes pregnant while taking the FDC, the patient should be apprised of the potential harm to the fetus.
There are no adequate and well-controlled studies of the FDC in pregnant women. The FDC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus, such as in pregnant women without other therapeutic options. [18]

It is recommended that all patients with HIV be tested for the presence of HBV before initiating antiretroviral therapy. The FDC is not indicated for the treatment of chronic HBV infection and the safety and efficacy of the FDC have not been established in patients co-infected with HBV and HIV. Severe acute exacerbations of hepatitis B have been reported in patients after the discontinuation of emtricitabine and tenofovir. Hepatic function should be closely monitored with both clinical and laboratory follow-up for at least several months in patients who discontinue the FDC and are co- infected with HIV and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted.[18]

Patients with creatinine clearance <50 mL/min should not receive the FDC.

Although the price of the FDC in developing countries has not yet been established, MSD makes STOCRIN (efavirenz) available at differential prices in these markets. Our intention is to use a similar approach by which the FDC will be made available in developing countries.

9. Treatment details

The efavirenz / emtricitabine / tenofovir DF fixed dose combination 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.[18]

Adults: The FDC is a fixed dose combination tablet containing 600 mg of efavirenz, 200 mg of emtricitabine, and 300 mg of tenofovir DF (which is equivalent to 245 mg of tenofovir disoproxil) as active ingredients. The dosage is one tablet of the FDC every day, taken orally on an empty stomach. [18]

Children: The FDC is not recommended for patients less than 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.[18]

Elderly: 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 drug therapy.[18]

Renal insufficiency: The FDC should not be prescribed for patients requiring dosage adjustment such as those with moderate or severe renal impairment (creatinine clearance <50 mL/min).[18]

Liver disease: The pharmacokinetics of efavirenz has not been adequately studied in patients with hepatic impairment. 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. 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 the FDC needs to be weighed against the unknown risks of significant liver toxicity. 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 the FDC to these patients.[18]

9.1. Duration

Antiretroviral treatment is usually regarded as life-long, with the exceptions of post-exposure prophylaxis and for the prophylaxis of infants of HIV-infected mothers.

9.2. Guidelines

The Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents issued by the United States Department of Health and Human Services (DHHS) guidelines (updated in May 2006) recommend that emtricitabine and tenofovir DF, the individual components of the fixed dose combination tablet, should be a component of first line ARV regimens containing EFV (DHHS Guidelines).[1] Similarly, the International AIDS Society-USA (IAS) Treatment Recommendations for Adult HIV Infection (updated in July 2004) recommend that emtricitabine and tenofovir DF should be a component of first line ARV regimens containing EFV and/or a boosted protease inhibitor.[2]

9.3. Special Requirements

Adequate resources for monitoring and specialist oversight are a pre-requisite for the introduction of this class of drugs.

10. Comparative effectiveness in clinical settings

Study 934: Emtricitabine + Tenofovir Disoproxil Fumarate + Efavirenz Compared with Zidovudine/Lamivudine + Efavirenz [20]

Data through 48 weeks are reported for Study 934, a randomized, open-label, active-controlled multicenter 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: 18–80), 86% were male, 59% were Caucasian and 23% were Black. The mean baseline CD4 cell count was 245 cells/mm^3 (range: 2–1191) and median baseline plasma HIV-1 RNA was 5.01 $\log_{10}$ copies/mL (range 3.56–6.54). 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 3.

Table 3. Outcomes of Randomized Treatment at Week 48 (Study 934) [20]

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, noncompliance, 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. [20]

ANRS 1207/IMEA 025 study: Emtricitabine + Tenofovir Disoproxil Fumarate + Efavirenz in Senegal [21]

A prospective open-label one-arm study has been performed in Senegal to evaluate the efficacy and tolerability of a simplified once-a-day highly active antiretroviral therapy regimen in adults. 40 treatment-naïve HIV-1-infected patients took the following three drugs emtricitabine, tenofovir and efavirenz once a day.

Results: Ninety-five per cent of patients were at Centers for Disease Control and Prevention stage B or C and the media plasma HIV RNA level was 5.3 [2.6-5.9] log10 copies/ml at baseline. The percentage of patients, with plasma HIV-1 RNA below 400 copies/ml and 50 copies/ml at week 48, was respectively 85% and 72% in an intent-to-treat analysis and respectively 94% and 83% in an on-treatment analysis. The median CD4 cell count was 122 [3-310] $x10^6$/l at baseline and increased by a mean of 185 $\pm$ 85 $x10^6$/l at week 48.

Conclusions: In this first evaluation in West Africa, this easy-to-take once-daily regimen of tenofovir, emtricitabine and efavirenz exhibited potent antiretroviral and immunological effect in patients even in this population with a very advanced disease. This regimen was well accepted, tolerated and majority of patients had a good level of adherence.

11. Comparative evidence on safety

11.1 Estimate of total patient exposure to date

Clinical Trials

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.

Post-Marketing

The first approval for the EFV/FTC/TDF fixed dose combination tablets have been granted by FDA on 12-july-2006.

However, in addition to adverse events reported from clinical trials, 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.

11.2 Descriptions of adverse effects/reactions

Clinical trials

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

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

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 (0–48 weeks)

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

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 coinfected patients, one patient (1/10) in the efavirenz, emtricitabine and tenofovir DF arm had elevations in ALT and AST to greater than five times ULN through 48 weeks. One patient (1/16) in the fixed-dose zidovudine/lamivudine arm had elevations in ALT to greater than five times 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 greater than five times ULN through 48 weeks. No HBV and/or HCV coinfected patient discontinued from the study due to hepatobiliary disorders

Post-Marketing

Efavirenz:

CARDIAC DISORDERS
Palpitations

EAR AND LABYRINTH DISORDERS
Tinnitus

ENDOCRINE DISORDERS
Gynecomastia

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, Hypercholesterolemia, Hypertriglyceridemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS
Arthralgia, Myalgia, Myopathy

NERVOUS SYSTEM DISORDERS
Abnormal coordination, Ataxia, Convulsions, Hypoesthesia, Paresthesia, Neuropathy, Tremor

PSYCHIATRIC DISORDERS
Aggressive reactions, Agitation, Delusions, Emotional lability, Mania, Neurosis, Paranoia, Psychosis, Suicide

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS
Dyspnea

SKIN AND SUBCUTANEOUS TISSUE DISORDERS
Flushing, Erythema multiforme, Nail disorders, Photoallergic dermatitis, Skin discoloration, 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
Hypophosphatemia, Lactic acidosis

RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS
Dyspnea

GASTROINTESTINAL DISORDERS

Abdominal pain, Increased amylase, Pancreatitis

HEPATOBILIARY DISORDERS
Increased liver enzymes, Hepatitis

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, Nephritis

11.2.1 Warnings and precautions for use

Lactic Acidosis/Severe Hepatomegaly with Steatosis

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. 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 analogs 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 transaminases elevations).

Patients with HIV and HBV Co-infection

It is recommended that all patients with HIV be tested for the presence of 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 after the discontinuation of EMTRIVA and VIREAD. Hepatic function should be closely monitored with both clinical and laboratory follow up for at least several months in patients who discontinue ATRIPLA and are coinfected with HIV and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

Co-administration with Related Drugs

Related drugs not for co-administration with the FDC include emtricitabine, tenofovir emtricitabine/tenofovir in co-formulation, and efavirenz, which contain the same active components as the FDC. Due to similarities between emtricitabine and lamivudine, the FDC should not be co-administered with drugs containing lamivudine.

Drug Interactions

Concomitant use of the FDC 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 suboptimal 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 1008 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%), nonfatal suicide attempts (0.5%, 0%), aggressive behavior (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 multifactor 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 drug 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 behavior, 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

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 depersonalization. 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 2–4 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. Dosing at bedtime may improve the tolerability of the nervous system.

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 the FDC should be alerted to the potential for additive central nervous system effects when the FDC is used concomitantly with alcohol or psychoactive drugs.

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

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

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported in association with the use of tenofovir DF. The majority of these cases occurred in patients with underlying systemic or renal disease, or in patients taking nephrotoxic agents; however, some cases occurred in patients without identified risk factors.

The FDC should be avoided with concurrent or recent use of a nephrotoxic agent. Patients at risk for, or with a history of, renal dysfunction and patients receiving concomitant nephrotoxic agents should be carefully monitored for changes in serum creatinine and phosphorus.

Reproductive Risk Potential

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

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

Efavirenz: As of July 2005, the Antiretroviral Pregnancy Registry has received prospective reports of 282 pregnancies exposed to efavirenz-containing regimens, nearly all of which were first-trimester exposures (277 pregnancies). Birth defects occurred in 5 of 228 live births (first-trimester exposure) and 1 of 14 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 preclinical studies of efavirenz.

Animal toxicology: 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 (post-coital days 20–150) with efavirenz 60 mg/kg daily, a dose which resulted in plasma drug concentrations similar to those in humans given 600 mg/day of efavirenz. Anencephaly and unilateral anophthalmia were observed in one fetus, microophthalmia was observed in another fetus, and cleft palate was observed in a third fetus. Efavirenz crosses the placenta in cynomolgus monkeys and produces fetal blood concentrations similar to maternal blood concentrations. Efavirenz has been shown to cross the placenta in rats and rabbits and produces fetal blood concentrations of efavirenz similar to maternal concentrations. An increase in fetal 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 600 mg once daily of efavirenz. 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 given 600 mg once daily of efavirenz.

12. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group

12.1. Range of costs of the proposed medicine

12.1.1 United States of America

ATRIPLA™ (efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) /Pack of 30 Tablets is commercialized by Bristol Myers Squibb and Gilead Sciences, at:

Ex- Gilead Sciences: $1,150.88

12.1.2 Developing Countries

The price of ATRIPLA™ in developing countries has not been established. As indicated in STOCRIN® 600 MG application, MSD makes STOCRIN® 600 MG available at differential prices in developing countries. MSD's intention is to use a similar approach by which ATRIPLA™ will be made available in developing countries.

13. Summary of regulatory status of the medicine (in country of origin and preferably in other countries as well):

ATRIPLA™ , the Efavirenz, emtricitabine and tenofovir DF fixed dose combination tablet, has been approved by US FDA on 12 july 2006.

The dossier has been filed to European authorities (EMEA) in October 2006.

Filing is planned in Access countries from November 2006 onward.

14. Availability of pharmacopoeial standards:

British Pharmacopoeia: no
International Pharmacopoeia: Efavirenz monograph was adopted at the Fortieth WHO Expert Committee on Specifications for Pharmaceutical Preparations in October 2005 for addition to the 4th edition of the International Pharmacopoeia.
United States Pharmacopoeia: no

15. Proposed (new/adapted) text for the WHO Model Formulary:

WHO Model Formulary 2007

Description:

The fixed dose combination tablet contains efavirenz, emtricitabine, and tenofovir disoproxil fumarate (tenofovir DF). Efavirenz is a non-nucleoside reverse transcriptase inhibitor, Emtricitabine, a synthetic nucleoside analog of cytidine and tenofovir DF, which is converted in vivo to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate.

How Supplied:

Each tablet contains 600 mg of efavirenz, 200 mg of emtricitabine, and 300 mg of tenofovir 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 sulfate. The tablets are film-coated with a coating material containing polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Use:

Efavirenz, emtricitabine and tenofovir DF fixed dose combination tablets (EFV/FTC/TDF tablets) are indicated for the treatment for HIV-1 infection in adults, alone as a complete regimen or in combination with other antiretroviral agents.

Contraindications:

EFV/FTC/TDF tablets is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the product.

EFV/FTC/TDF tablets should not be administered concurrently with astemizole, cisapride, midazolam, triazolam 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). EFV/FTC/TDF tablets should not be administered concurrently with voriconazole because efavirenz significantly decreases voriconazole plasma concentrations.

Warnings:

Lactic Acidosis/Severe Hepatomegaly with Steatosis

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. 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 analogs 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 EFV/FTC/TDF tablets 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).

Patients with HIV and HBV Coinfection

It is recommended that all patients with HIV be tested for the presence of HBV before initiating antiretroviral therapy. EFV/FTC/TDF tablet is not indicated for the treatment of chronic HBV infection and the safety and efficacy of EFV/FTC/TDF tablets have not been established in patients co-infected with HBV and HIV. Severe acute exacerbations of hepatitis B have been reported in patients after the discontinuation of emtricitabine and tenofovir DF. Hepatic function should be closely monitored with both clinical and laboratory follow up for at least several months in patients who discontinue EFV/FTC/TDF tablets and are coinfected with HIV and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

Coadministration with Related Drugs

Related drugs not for coadministration with EFV/FTC/TDF tablets are each of the individual components of the fixed dose combination. Due to similarities between emtricitabine and lamivudine, ATRIPLA should not be coadministered with drugs containing lamivudine.

Precautions:

Drug Interactions

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 drugs primarily metabolized by these isozymes may result in altered plasma concentrations of the co-administered drug. Therefore, appropriate dose adjustments may be necessary for these drugs.

Drugs which induce CYP3A4 activity (eg, 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 EFV/FTC/TDF tablets with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of emtricitabine, tenofovir, and/or other renally eliminated

drugs. Some examples include, but are not limited to, adefovir dipivoxil, cidofovir, acyclovir, valacyclovir, ganciclovir, 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**).**

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. EFV/FTC/TDF tablets should be discontinued in patients who develop tenofovir-associated adverse events (for atazanavir dosing adjustment recommendations**)**.

Other important drug interaction information for EFV/FTC/TDF tablets is summarized in Table 6 and 7. The drug interactions described are based on studies conducted with efavirenz, emtricitabine or tenofovir DF as individual agents or are potential drug interactions; no drug interaction studies have been conducted using EFV/FTC/TDF tablets. The tables include potentially significant interactions, but are not all inclusive.

Table 6. Drugs That Are Contraindicated or Not Recommended for Use With EFV/FTC/TDF tablets

Drug Class: Drug 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. See Tables 1 and 2.
Antihistamine: astemizole	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antimigraine: ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine)	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
Antiretrovirals: EMTRIVA, VIREAD, TRUVADA, SUSTIVA, STOCRIN, COMBIVIR, EPIVIR, EPIVIR-HBV, EPZICOM, TRIZIVIR	Not for use with EFV/FTC/TDF tablets because the active ingredients of EMTRIVA (emtricitabine), VIREAD (tenofovir DF), TRUVADA (emtricitabine/tenofovir DF) and SUSTIVA or STOCRIN (efavirenz) are components of ATRIPLA. Lamivudine, which is similar to emtricitabine, is a component of COMBIVIR, EPIVIR, EPIVIR-HBV, EPZICOM, and TRIZIVIR.
Benzodiazepines: midazolam, triazolam	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.
GI motility agent: cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
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 7. Established[1] and Other Potentially Significant[2] Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect	Clinical Comment
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 plus ritonavir twice daily.
Protease inhibitor: Atazanavir	↓ atazanavir concentration ↑ tenofovir concentration	Plasma concentrations of atazanavir were decreased by both efavirenz and tenofovir DF. Sufficient data are not available to make a dosing recommendation for atazanavir or atazanavir/ritonavir with ATRIPLA. Therefore, co-administration of ATRIPLA and atazanavir is not recommended due to concerns regarding decreased atazanavir concentrations.
Protease inhibitor: Indinavir	↓ indinavir concentration	The optimal dose of indinavir, when given in combination with efavirenz, is not known. Increasing the indinavir dose to 1000 mg every 8 hours does not compensate for the increased indinavir metabolism due to efavirenz.
Protease inhibitor: Lopinavir/ritonavir	↓ lopinavir concentration ↑ tenofovir concentration	A dose increase of lopinavir/ritonavir to 600/150 mg (3 tablets) twice daily may be considered when used in combination with efavirenz in treatment-experienced patients where decreased susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). **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 concentration	When ritonavir 500 mg every 12 hours was co-administered with efavirenz 600 mg once daily, the combination was associated with a higher frequency of adverse clinical experiences (eg, dizziness, nausea, paresthesia) and laboratory abnormalities (elevated liver enzymes). Monitoring of liver enzymes is recommended when ATRIPLA is used in combination with ritonavir.
Protease inhibitor: Saquinavir	↓ saquinavir concentration	Should not be used as sole protease inhibitor in combination with EFV/FTC/TDF tablets.

Concomitant Drug Class: Drug Name	**Effect**	**Clinical Comment**
NRTI: Didanosine	↑ didanosine concentration	Higher didanosine concentrations could potentiate didanosine-associated adverse events, including pancreatitis, and neuropathy. **In adults weighing >60 kg, the didanosine dose should be reduced to 250 mg if co-administered with EFV/FTC/TDF tablets**. **Data are not available to recommend a dose adjustment of didanosine for patients weighing <60 kg.** When co-administered, EFV/FTC/TDF tablets and VIDEX® EC may be taken under fasted conditions or with a light meal (<400 kcal, 20% fat). Co-administration of didanosine buffered formulation with EFV/FTC/TDF tablets should be under fasted conditions. **Co-administration of EFV/FTC/TDF tablets and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse events. For additional information, please consult the Videx / Videx EC (didanosine) prescribing information.**
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 EFV/FTC/TDF tablets. 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.

Concomitant Drug Class: Drug Name	Effect	Clinical Comment
Antifungals: Itraconazole Ketoconazole	↓ antifungal concentration	Drug interaction studies with EFV/FTC/TDF tablets and these imidazole and triazole antifungals have not been conducted. Efavirenz has the potential to decrease plasma concentrations of itraconazole and 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 EFV/FTC/TDF tablets 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 EFV/FTC/TDF tablets.
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: Rifampin	↓ efavirenz concentration	Clinical significance of reduced efavirenz concentrations is unknown.
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 prescribing information for the HMG-CoA reductase inhibitor for guidance on individualizing the dose.
Narcotic analgesic: Methadone	↓ methadone concentration	Co-administration of efavirenz in HIV-infected individuals with a history of injection drug use resulted in decreased plasma levels of methadone and signs of opiate withdrawal. Methadone dose was increased by a mean of 22% to alleviate withdrawal symptoms. Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.
Oral contraceptive: Ethinyl estradiol	↑ ethinyl estradiol concentration	Clinical significance unknown. Because the potential interaction of efavirenz with oral contraceptives has not been fully characterized, a reliable method of barrier contraception should be used in addition to oral contraceptives.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Efavirenz did not impair mating or fertility of male or female rats, and did not affect sperm 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 equivalent to or below those achieved in humans given therapeutic doses of efavirenz.

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

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

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

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

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

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

Pregnancy
Pregnancy Category D (see *Error! Reference source not found.****,***
Reproductive Risk Potential)
Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal 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 breast-feed if they are receiving EFV/FTC/TDF tablets**.

Pediatric Use

EFV/FTC/TDF tablet is not recommended for patients less than 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 drug therapy.

Adverse Effects:

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, psychiatric symptoms, and 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, paresthesia, 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 discoloration has been reported with higher frequency among emtricitabine treated patients. 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 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 8.

Table 8. Selected Treatment-Emergent Adverse Events (Grades 2–4) Reported in ≥3% in Any Treatment Group in Study 934 (0–48 weeks)

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

Laboratory Abnormalities: Laboratory abnormalities observed in this study were generally consistent with those seen in other studies (Table 9).

Table 9. Significant Laboratory Abnormalities Reported in ≥1% in Any Treatment Group in Study 934 (0–48 weeks)

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

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 greater than five times ULN through 48 weeks. One patient (1/16) in the fixed-dose zidovudine/lamivudine arm had elevations in ALT to greater than five times 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 greater than five times ULN through 48 weeks. No HBV and/or HCV co-infected patient discontinued from the study due to hepatobiliary disorders

Post Marketing Experience

In addition to adverse events reported from clinical trials, 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
Gynecomastia

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** Error! Reference source not found.**,** Error! Reference source not found.**)**, Hypercholesterolemia, Hypertriglyceridemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS
Arthralgia, Myalgia, Myopathy

NERVOUS SYSTEM DISORDERS
Abnormal coordination, Ataxia, Convulsions, Hypoesthesia, Paresthesia, Neuropathy, Tremor

PSYCHIATRIC DISORDERS
Aggressive reactions, Agitation, Delusions, Emotional lability, Mania, Neurosis, Paranoia, Psychosis, Suicide

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS
Dyspnea

SKIN AND SUBCUTANEOUS TISSUE DISORDERS
Flushing, Erythema multiforme, Nail disorders, Photoallergic dermatitis, Skin discoloration, 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
Hypophosphatemia, Lactic acidosis

RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS
Dyspnea

GASTROINTESTINAL DISORDERS
Abdominal pain, Increased amylase, Pancreatitis

HEPATOBILIARY DISORDERS
Increased liver enzymes, Hepatitis

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, Nephritis

Dosage and Administration

Adults: The dose of EFV/FTC/TDF fixed dose combination is one tablet once daily taken orally on an empty stomach. Dosing at bedtime may improve the tolerability of nervous system symptoms.

Pediatrics: EFV/FTC/TDF fixed dose combination is not recommended for use in patients <18 years of age.

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

References:

1. UNAIDS/World Health Organization. AIDS epidemic update: December 2005, December 2005.

2. Joint United Nations Programme on HIV/AIDS (UNAIDS). Global summary of the HIV and AIDS epidemic, December 2005 [PowerPoint Presentation]. Available at: http://www.unaids.org/en/HIV_data/Epidemiology/epi_slides.asp.

3. UNAIDS/World Health Organization. HIV infection rates decreasing in several countries but global number of people living with HIV continues to rise [press release] November 21 2005.

4. Joint United Nations Programme on HIV/AIDS (UNAIDS). Executive Summary. 2004 Report on the global AIDS epidemic. Switzerland: UNAIDS; June 2004.

5. UNAIDS/World Health Organization. AIDS epidemic update: December 2003 December 2003.

6. Palella FJ, Jr, Delaney KM, Moorman AC, *et al.* Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med.* 1998;338(13):853-860.

7. Department of Health and Human Services (DHHS). Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.
October 10, 2006. Available at: http://AIDSinfo.nih.gov

8. World Health Organization (WHO). Antiretroviral Therapy for HIV Infection in Adults and Adolescents in Resource-limited settings: Toward
Universal Access . Recommendations for a public health approach - 2006 revision, Geneva, Switzerland: World Health Organization; 2006

9. The British HIV Association. Draft BHIVA guidelines for the treatment of HIV-infected adults with antiretroviral therapy (2006). Available at: http://www.bhiva.org

10. Salzberger B, Marcus U, Vielhaber B, Arasteh K, Golz J, Brockmeyer NH, *et al.*German-Austrian recommendations for the antiretroviral therapy of HIV-infection (status May 2004). Eur J Med Res 2004;9 (11):491-504**.**

11. Ministero Della Salute Terapia Antiretrovirale. Aggiornamento Sulle Conoscenze In Tema Di Terapia Antiretrovirale, 2 Edizione. Documento elaborato dalla Commissione Nazionale per la lotta contro l'AIDS - Comitato Scientifico di Progetto del Centro Nazionale per la Prevenzione e il controllo delle malattie. GioFil – Banca Dati Sanitaria Farmaceutica Dicembre, 2005.

12. Iribarren JA, Labarga P, Rubio R, Berenguer J, Miro JM, Antela A, *et al*. Recomendaciones De GESIDA/Plan Nacional Sobre El Sida Respecto Al
Tratamiento Antirretroviral En Pacientes Adultos Infectados Por El Virus De La Inmunodeficiencia Humana. Diciembre, 2005.

13. Recommandations du groupe d'experts - Sous la direction du Professeur Patrick Yeni. Prise en charge médicale des personnes
infectées par le VIH. Rapport 2006. Réalisé avec le soutien du Ministère de la Santé et des Solidarités. Editions Flammarion SA. Juillet 2006. Available at: http://www.sante.gouv.fr

14. Hammer SM, Saag MS, Schechter M, Montaner JSG, Schooley RT, Jacobsen DM, *et al.* Treatment for adult HIV infection: 2006 recommendations of the International AIDS Society-USA panel. JAMA 2006;296 (7):827-43.

15. World Health Organization (WHO).Access to HIV/AIDS Drugs and Diagnostics of Acceptable Quality. Version: 40th Edition, 14 August 2006.
Available at http://mednet3.who.int/prequal/lists/hiv_suppliers.pdf

16. Jose R. Arribas. Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate Triple Combination Tablet. Drugs 2006; 66 (11): 1513, 2006

17. Paul Volberding. Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate Triple Combination Tablet. Drugs 2006; 66 (11): 1513-1514, 2006

18. ATRIPLA ® USPC approved by FDA on july 12th,2006.

19. World Health Organization (WHO). Accelerating Access Initiative - Widening access to care and support for people living with HIV/AIDS - Progress Report, June 2002, Geneva, Switzerland: World Health Organization; 2002

20. Gallant JE, DeJesus E, Arribas JR, *et al*. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *N Engl J Med.* Jan 19 2006;354(3):251-260.

21. Landman R, Diallo M, Diakhate N, *et al.* Evaluation of TDF/FTC/EFV once daily first line regimen in West Africa. ANRS 1207/IMEA 025 trial [poster board 543]. Paper presented at: 13th Conference on Retroviruses and Opportunistic Infections; February 5-9, 2006; Denver, Colorado, USA.