Product Monograph

PrATRIPLA®

(efavirenz/emtricitabine/ tenofovir disoproxil fumarate) tablets

600 mg efavirenz
200 mg emtricitabine
300 mg tenofovir disoproxil fumarate

Antiretroviral Agent

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PART I. HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Nonmedicinal Ingredients[a]
Oral	Tablet efavirenz 600 mg/ emtricitabine 200 mg/ tenofovir disoproxil fumarate 300 mg	None

a. For a complete listing, see the DOSAGE FORMS, COMPOSITION, AND PACKAGING section.

INDICATIONS AND CLINICAL USE

ATRIPLA® (efavirenz [EFV]/emtricitabine [FTC]/tenofovir disoproxil fumarate [TDF]) 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. **(**see **CLINICAL TRIALS, Description of Clinical Studies** and **ADVERSE REACTIONS)**.

Geriatrics (>65 years of age):
Clinical studies of the components of ATRIPLA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Pediatrics (<18 years of age):
Safety and effectiveness in pediatric patients have not been established. ATRIPLA is not recommended for pediatric administration.

CONTRAINDICATIONS

ATRIPLA is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the product. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

Competition for CYP3A4 by EFV could result in inhibition of metabolism of some drugs and create the potential for serious and/or life-threatening adverse events. Drugs that are contraindicated with ATRIPLA are listed in Table 1. See also **DRUG INTERACTIONS, Drug-Drug Interactions.**

Table 1. Drugs That Are Contraindicated with ATRIPLA

Drug Class: Drug Name	Clinical Comment
Antiarrhythmics: bepridil*	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
HCV antiviral agents: elbazvir/grazoprevir	CONTRAINDICATED due to the expected significant decreases in plasma concentrations of elbasvir and grazoprevir. This effect is due to induction of CYP3A4 by efavirenz, and may result in loss of therapeutic effect.
Antifungal: voriconazole	CONTRAINDICATED because EFV significantly decreases voriconazole plasma concentrations, and coadministration may decrease the therapeutic effectiveness of voriconazole. Also, voriconazole significantly increases EFV plasma concentrations, which may increase the risk of EFV-associated side effects. Because ATRIPLA is a fixed dose combination product, the dose of EFV cannot be altered; therefore, voriconazole and ATRIPLA cannot be coadministered.
Antihistamines: astemizole*, terfenadine*	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.
Benzodiazepines: midazolam, triazolam	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.
Neuroleptic: pimozide	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
GI motility agent: cisapride*	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal products: St. John's wort (*Hypericum perforatum*)	CONTRAINDICATED due to risk of reduced plasma concentrations of EFV. This effect is due to an induction of CYP3A4 and may result in loss of virologic response and possible resistance to EFV or to the class of non-nucleoside reverse transcriptase inhibitors (NNRTIs).

*Not marketed in Canada.

WARNINGS AND PRECAUTIONS

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs including VIREAD, a component of ATRIPLA, alone or in combination with other antiretrovirals **(**see **WARNINGS AND PRECAUTIONS: Hepatic/Biliary/Pancreatic)**.

ATRIPLA is not approved for the treatment of chronic hepatitis B virus (HBV) infection and the safety and efficacy of ATRIPLA have not been established in patients coinfected with HBV and HIV. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV after the discontinuation of EMTRIVA® or VIREAD®, two of the components of ATRIPLA. In some patients infected with HBV and treated with EMTRIVA, the exacerbations of hepatitis B were associated with liver decompensation and liver failure. 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 **(**see **WARNINGS AND PRECAUTIONS: Special Populations)**.

Renal failure, renal insufficiency, elevated creatinine, hypophosphatemia, and Fanconi syndrome have been reported with the use of TDF during clinical practice **(**see **WARNINGS AND PRECAUTIONS)**.

General

ATRIPLA should not be administered with the following related drugs including COMPLERA® (FTC/rilpivirine/TDF), EMTRIVA® (FTC), TRUVADA® (FTC/TDF), STRIBILD® (elvitegravir/cobicistat/FTC/TDF) and VIREAD® (TDF).

Due to similarities between FTC and lamivudine, ATRIPLA should not be administered with drugs containing lamivudine including Combivir® (lamivudine/zidovudine), 3TC® (lamivudine), Heptovir® (lamivudine), Kivexa® (abacavir/lamivudine), Triumeq® (dolutegravir/abacavir/lamivudine) and Trizivir® (abacavir/lamivudine/zidovudine).

ATRIPLA should not be administered concurrently with drugs containing tenofovir alafenamide (TAF) including DESCOVY® (FTC/TAF), GENVOYA® (elvitegravir/cobicistat/FTC/TAF), ODEFSEY™ (FTC/rilpivirine/TAF), or VEMLIDY™ (TAF).

ATRIPLA should not be administered with HEPSERA® (adefovir dipivoxil).

ATRIPLA should not be administered with Sustiva® (EFV) unless needed for dose-adjustment of EFV (e.g., with rifampin) (see **DRUG INTERACTIONS**).

Clinical trial data of patients who were switched to ATRIPLA from a prior PI-containing regimen suggest that they may have lower response rates than patients who remain on their baseline regimens (see **CLINICAL TRIALS** section). Therefore, patients who are switched to ATRIPLA from a prior PI-containing regimen should be monitored for both treatment-emergent adverse events and rises in viral load.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Efavirenz:
Oral carcinogenicity studies in mice and rats were carried out with EFV. 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 at all doses were increased above background in females. No increases in tumor incidence above background were seen in males. The systemic exposure (based on AUCs) in mice was approximately 1.7-fold that in humans receiving the 600-mg/day dose. Rats were administered EFV at doses of 0, 25, 50, or 100 mg/kg/day for 2 years; no increases in tumor incidence above background were observed. The exposure in rats was lower than that in humans.

The mechanism of the carcinogenic potential is unknown. However, in genetic toxicology assays, EFV 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 EFV, the relevance to humans of neoplasms in EFV-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 EFV was not affected. As a result of the rapid clearance of EFV in rats, systemic drug exposures achieved in these studies were equivalent to or below those achieved in humans given therapeutic doses of EFV.

Emtricitabine:
In long-term oral carcinogenicity studies of FTC, no drug-related increase in tumor incidence was 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/kg/day (31 times the human systemic exposure at the therapeutic dose).

Emtricitabine was not genotoxic in the in vitro reverse mutation bacterial test (Ames test), or in vivo 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:
Tenofovir disoproxil fumarate did not show any carcinogenic potential in a long-term oral carcinogenicity study in rats. A long-term oral carcinogenicity study in mice showed a low incidence of duodenal tumors, considered likely related to high local concentrations in the

gastrointestinal tract at the high dose of 600 mg/kg/day. The mechanism of tumor formation in mice and potential relevance for humans is uncertain.

Tenofovir disoproxil fumarate 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, TDF was negative at doses up to 2000 mg/kg when administered orally to male mice.

There were no effects on fertility, mating performance or early embryonic development when TDF was administered at 600 mg/kg/day to male rats 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. A dose of 600 mg/kg/day is equivalent to 19 times the human dose based on body surface area comparisons.

Cardiovascular

QTc Prolongation:
QTc prolongation has been observed with the use of EFV (see **DRUG INTERACTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**). Consider alternatives to ATRIPLA when coadministered with a drug with a known risk of Torsade de Pointes or when administered to patients at higher risk of Torsade de Pointes.

Drug Interactions

Use with Certain HCV Regimens:
Tenofovir exposure is increased when ATRIPLA is coadministered with HARVONI® (ledipasvir/sofosbuvir). Patients receiving ATRIPLA concomitantly with HARVONI, particularly those at increased risk for renal dysfunction, should be monitored for tenofovir-associated adverse reactions (see **DRUG INTERACTIONS**).

Coadministration of EFV with a HCV treatment regimen containing velpatasvir has been shown to decrease velpatasvir exposure. Coadministration of ATRIPLA with EPCLUSA® (sofosbuvir/velpatasvir) resulted in increased tenofovir exposure and decreased velpatasvir exposure. Tenofovir exposure is expected to increase and velpatasvir and voxilaprevir are expected to decrease upon coadministration of VOSEVI™ (sofosbuvir/velpatasvir/voxilaprevir) and ATRIPLA. Coadministration of ATRIPLA with EPCLUSA or VOSEVI is not recommended (see **DRUG INTERACTIONS**).

Effects On Ability To Drive and To Use Machines

ATRIPLA may cause dizziness, impaired concentration, and/or drowsiness, due to the EFV component. Patients should be instructed that, if they experience these symptoms, they should avoid potentially hazardous tasks such as driving or operating machinery (see **WARNINGS AND PRECAUTIONS: Neurologic**).

Endocrine and Metabolism

Serum Lipids and Blood Glucose:
Serum lipid and blood glucose levels may increase during antiretroviral therapy. Disease control and life style changes may also be contributing factors. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders and blood glucose elevations should be managed as clinically appropriate.

Hepatic/ Biliary/Pancreatic

Lactic Acidosis/Severe Hepatomegaly with Steatosis:
Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogs including the TDF component of ATRIPLA, alone or in combination with other antiretrovirals in the treatment of HIV infection. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside 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 transaminase elevations).

Hepatotoxicity – EFV:
Postmarketing reports of hepatic failure have occurred in patients receiving EFV, including some cases in patients without pre-existing hepatic disease or other identifiable risk factors (see **WARNINGS AND PRECAUTIONS**, **Monitoring and Laboratory Tests** and **ADVERSE REACTIONS**, **Post-Market Adverse Drug Reactions**).

In patients with persistent elevations of serum transaminases to greater than five times the upper limit of the normal range, the benefit of continued therapy with ATRIPLA needs to be weighed against the potential risks of significant liver toxicity.

Hepatic Impairment:
The pharmacokinetics of EFV has not been adequately studied in patients with hepatic impairment. ATRIPLA is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) because of insufficient data. Caution should be exercised in administering ATRIPLA to patients with mild hepatic impairment because of the extensive cytochrome P450-mediated metabolism of EFV and limited clinical experience. Patients should be monitored carefully for adverse events, and laboratory tests to evaluate the

liver disease should be performed at periodic intervals. (See **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, DOSAGE AND ADMINISTRATION; Dose Adjustment for Hepatic Impairment**, and **ACTION AND CLINICAL PHARMACOLOGY; Pharmacokinetics: Special Populations and Conditions**).

Tenofovir and tenofovir disoproxil are not metabolized by liver enzymes. Clinically relevant pharmacokinetic changes in patients with hepatic impairment are not observed. Emtricitabine has not been evaluated in patients with hepatic impairment; however, FTC has not been shown to be metabolized by liver enzymes, so the impact of liver impairment is likely to be limited.

The safety and efficacy of ATRIPLA have not been established or specifically studied in patients with underlying liver disorders. Patients with chronic hepatitis B or C and treated with antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products **(**see **WARNINGS AND PRECAUTIONS: Special Populations)**.

Pancreatitis:
Pancreatitis has occurred during therapy with combination regimens that included TDF. Caution should be used when administering nucleoside analogues (including ATRIPLA) to patients with a history of pancreatitis or risk factors for the development of pancreatitis. Therapy should be suspended in patients with suspected pancreatitis.

In controlled clinical studies the rate of clinical pancreatitis was similar in patients receiving [1/1008 (0.1%)] and not receiving [2/635 (0.3%)] EFV. Asymptomatic increases in serum amylase levels were observed in a significantly higher number of patients treated with EFV 600 mg than in control patients.

Elevated triglycerides have been reported in patients receiving EFV, in some cases to levels which can predispose a patient to pancreatitis. Among patients with elevated triglycerides, there have been no cases of pancreatitis. Because these triglyceride levels were not obtained in a fasting state, the exact clinical relevance of these measurements is not known.

Immune

Hypersensitivity Reactions:
In clinical trials, hypersensitivity reactions were uncommon (<1%) in patients treated with EFV.

Immune Reconstitution Inflammatory Syndrome:

Immune Reconstitution Inflammatory Syndrome has been reported in patients treated with combination antiretroviral therapy, including the components of ATRIPLA. During the initial phase of treatment, patients responding to antiretroviral therapy may develop an

inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infections, cytomegalovirus, *Pneumocystis jiroveci* pneumonia (PCP), and tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis and Guillain-Barre syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment.

Musculoskeletal

Bone Effects:
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.

In a 144 week study of treatment-naïve patients, decreases from baseline 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 in the TDF+lamivudine+EFV group compared with patients in the stavudine+lamivudine+EFV group. Changes in BMD at the hip were similar in the two treatment groups. In both groups, the majority of the reduction in BMD occurred in the first 24–48 weeks of the study and this reduction was sustained through Week 144. Twenty-eight percent of TDF-treated patients vs. 21% of the stavudine-treated 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 TDF group and 6 patients in the stavudine group. In addition, there were significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide, and urinary N-telopeptide) in the TDF group relative to the stavudine group, suggesting increased bone turnover. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in the TDF group. Except for bone specific alkaline phosphatase, these changes resulted in values that remained within the normal range. The effects of TDF-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown.

Cases of osteomalacia (associated with proximal renal tubulopathy and infrequently contributing to fractures) have been reported in association with the use of TDF (see **ADVERSE REACTIONS, Post Market Adverse Drug Reactions: Tenofovir disoproxil fumarate**).

For additional information, please consult the VIREAD Product Monograph.

Neurologic

Nervous System Symptoms:
Fifty-three percent (531/1008) of patients receiving EFV in controlled clinical trials reported central nervous system symptoms (any grade, regardless of causality) compared to 25% (156/635) of patients receiving control regimens. These symptoms included, but were not limited to, dizziness (28.1% of the 1008 patients), 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. After 4 weeks of therapy the prevalence of nervous system symptoms of at least moderate severity ranged from 5–9% in patients treated with regimens containing EFV and from 3–5% in patients treated with a control regimen. Patients should be informed that these symptoms are likely to improve with continued therapy. Dosing at bedtime improves tolerability of these symptoms.

Analysis of long-term data from a clinical study, (median follow-up 180 weeks, 102 weeks, and 76 weeks for patients treated with EFV+zidovudine+lamivudine, EFV+indinavir, and indinavir+zidovudine+lamivudine, respectively) showed that, beyond 24 weeks of therapy, the incidences of new-onset nervous system symptoms among EFV-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, due to the EFV component, when ATRIPLA is used concomitantly with alcohol or psychoactive drugs.

Seizures:
Caution should be taken in any patient with any history of seizures. Convulsions have been observed infrequently in patients receiving EFV, generally in the presence of known medical history of seizures. Overall, the rate of seizure in controlled clinical trials has been 0.89% in EFV treated patients and 0.63% in the control patients. Patients who are receiving concomitant anticonvulsant medications primarily metabolized by the liver such as phenytoin, carbamazepine, and phenobarbital, may require periodic monitoring of plasma levels (See **DRUG INTERACTIONS**).

Psychiatric

Serious psychiatric adverse reactions have been reported in patients treated with EFV. In controlled trials of 1008 patients treated with regimens containing EFV for an average of 2.1 years and 635 patients treated with control regimens for an average of 1.5 years, the frequency (regardless of causality) of specific serious psychiatric events among patients who received EFV 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 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 multifactorial analysis of data from a clinical study, treatment with EFV 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 EFV and control treatment groups. In Study 006, onset of new serious psychiatric symptoms occurred throughout the study for both EFV-treated and control-treated patients. One percent of EFV-treated patients discontinued or interrupted treatment because of one or more of these selected psychiatric symptoms. There have also been occasional postmarketing reports of death by suicide, delusions, psychosis-like behavior, and catatonia, although a causal relationship to the use of EFV cannot be determined from these reports. Patients with serious psychiatric adverse experiences should seek immediate medical evaluation to assess the probability that the symptoms may be related to the use of ATRIPLA, and if so, to determine whether the risks of continued therapy outweigh the benefits.

Renal

Nephrotoxicity:
Emtricitabine and tenofovir are principally eliminated by the kidney, however EFV 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.

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 TDF **(**see **ADVERSE REACTIONS, Post Marketing Experience).** 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.

It is recommended that creatine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with ATRIPLA. Routine monitoring of calculated creatine clearance and serum phosphorus should be performed in patients at risk for renal impairment, including patients who have previously experienced renal events while receiving HEPSERA.

ATRIPLA should be avoided with concurrent or recent use of a nephrotoxic agent. Examples of nephrotoxic agents include but are not limited to aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir, or interleukin-2. Particular caution should be exercised when administering ATRIPLA to patients with known risk factors for renal disease and a history of renal dysfunction; however, cases of renal failure have also been reported in patients with no known risk factors.

Skin

Rash:
ATRIPLA, due to its EFV component, is not recommended for patients who have had any life-threatening cutaneous reaction (e.g., Stevens-Johnson syndrome). ATRIPLA should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. Resumption of therapy with ATRIPLA after resolution of severe rash should be considered only if the benefit outweighs the risk, such as for patients without other therapeutic options. For Grade 1 or 2 rash (National Cancer Institute Grading System), appropriate antihistamines and /or corticosteroids may improve the tolerability and hasten the resolution of rash. ATRIPLA can be reinitiated in patients interrupting therapy due to Grades 1 and 2 rash.

In controlled clinical trials, 26% (266/1008) of patients treated with 600 mg EFV 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% (9/1008) of patients treated with EFV. Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first 2 weeks of initiating therapy with EFV (median time to onset of rash in adults was 11 days) and in most patients continuing therapy with EFV, rash resolves within 1 month (median duration, 16 days). The discontinuation rate for rash in clinical trials was 6.4% (17/266) among patients with rash and 1.7% (17/1008) overall.

Grade 4 rash (including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and exfoliative dermatitis) was uncommon (<1%) in patients treated with EFV in clinical studies.

Experience with EFV 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 EFV. Nine of these patients developed mild-to-moderate rash while receiving therapy with EFV, and two of these patients discontinued because of rash.

Special Populations

Patients with HIV and Hepatitis B Virus Coinfection:
It is recommended that all patients with HIV be tested for the presence of HBV before initiating antiretroviral therapy. ATRIPLA is not approved 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 coinfected with HBV and HIV after the discontinuation of EMTRIVA and VIREAD, two of the components of ATRIPLA. In some patients infected with HBV and treated with EMTRIVA, the exacerbations of hepatitis B were associated with liver decompensation and liver failure. 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 co-infected with HIV and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, post-treatment exacerbation of hepatitis may lead to hepatic decompensation. Therefore, in

these patients, discontinuation of treatment without initiation of alternative anti-hepatitis B therapy is not recommended.

Pregnant Women:
Efavirenz may cause fetal harm when administered during the first trimester to a pregnant woman. Pregnancy should be avoided in women receiving ATRIPLA and for 12 weeks after discontinuation. Barrier contraception must always be used in combination with other methods of contraception (e.g., oral or other hormonal contraceptives) (see **DRUG INTERACTIONS** and **TOXICOLOGY**). Because of the long half-life of EFV, use of adequate contraceptive measures for 12 weeks after discontinuation of ATRIPLA is recommended. Women of childbearing potential should undergo pregnancy testing prior to initiation of ATRIPLA.

There are no adequate and well-controlled studies in pregnant women. ATRIPLA should be used in pregnant women only if the potential benefits outweigh the potential risks to the fetus, such as in pregnant women without other therapeutic options.

Efavirenz: As of July 2013, the Antiretroviral Pregnancy Registry has received prospective reports of 1067 pregnancies exposed to EFV-containing regimens, 904 of which were first-trimester exposures. Birth defects occurred in 18 of 766 live births (first-trimester exposure) and 3 of 160 live births (second-/third-trimester exposure). One of these prospectively reported defects with first-trimester exposure was a neural tube defect. A single case of anophthalmia with first-trimester exposure to EFV has also been prospectively reported; however, this case included severe oblique facial clefts and amniotic banding, a known association with anophthalmia. There have been seven reports during post-marketing use of findings consistent with neural tube defects, including meningomyelocele, all in mothers exposed to EFV-containing regimens (excluding any EFV-containing fixed-dose combination) in the first trimester. Although a causal relationship of these events to the use of EFV cannot be established, similar defects have been observed in nonclinical studies of EFV (see **TOXICOLOGY**, **Reproductive Toxicology**).

Emtricitabine: The incidence of fetal variations and malformations was not increased in embryo-fetal toxicity studies performed with FTC in mice at exposures (AUC) approximately 60-fold higher and in rabbits at approximately 120-fold higher than human exposures at the recommended daily dose.

Tenofovir disoproxil fumarate: Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir. Reduced pup body weights, survival and delay in sexual maturation was observed in a peri- and postnatal toxicity study in rats at the maternally toxic doses of 450 and 600 mg/kg (approximately 14 and 19 times the human dose based on body surface area comparisons).

Antiretroviral Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to ART (antiretroviral therapy) including ATRIPLA, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients,
http://www.apregistry.com
Telephone: (800) 258–4263
Fax: (800) 800-1052

Nursing Women:

HIV-1 infected mothers should not breast-feed their infants to avoid risking postnatal transmission of HIV. Studies in rats have demonstrated that EFV is excreted in milk. Efavirenz has also been shown to pass into human breast milk. In humans, samples of breast milk obtained during the first week post-partum from five HIV-1 infected mothers who were dosed with FTC 200 mg and tenofovir 300 mg show that both tenofovir and FTC are secreted in human milk. Nursing infants whose mothers are being treated with ATRIPLA may be at risk for developing viral resistance to FTC. Tenofovir-associated risks (including the risk of developing viral resistance to tenofovir) and other FTC-associated risks in such infants are unknown. 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 ATRIPLA.**

Pediatrics (<18 years of age): Safety and effectiveness in pediatric patients have not been established. ATRIPLA is not recommended for pediatric administration.

Geriatrics (>65 years of age): Clinical studies of EFV, FTC or TDF did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. In general, dose selection for the elderly patient should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Monitoring and Laboratory Tests

Liver Enzymes: Monitoring of liver enzymes before and during treatment is recommended for patients with underlying hepatic disease, including hepatitis B or C infection; patients with marked transaminase elevations; and patients treated with other medications associated with liver toxicity. Liver enzyme monitoring should also be considered for patients without pre-existing hepatic dysfunction or other risk factors. (See **ADVERSE REACTIONS: Laboratory Abnormalities and WARNINGS AND PRECAUTIONS: Hepatic/Biliary/Pancreatic)**.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should

not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse Drug Reaction Overview

The combination of EFV+FTC+TDF has been studied in 460 patients either as the fixed-dose dose combination tablet ATRIPLA (Study 073) or as the component products (Study 934). Adverse reactions observed in Study 934 (Phase III) and Study 073 (Phase IV) were generally consistent with those seen in previous studies of the individual components.

The most common adverse events reported in Study 934 associated with study regimen of EFV+FTC+TDF through Week 144 were dizziness (25%), nausea (18%), and abnormal dreams (17%). Study regimen was discontinued due to an adverse event for 5% of subjects (13/257) in the EFV+FTC+TDF group and 11% of subjects (29/254) in the lamivudine/zidovudine+EFV group.

In study 073, the most frequently reported adverse events associated with ATRIPLA among patients treated up to 48 weeks were psychiatric disorders (16%); nervous system disorders (13%); and gastrointestinal disorders (7%). The majority of adverse events associated with ATRIPLA were mild in severity with dizziness (11%) and abnormal dreams (7%) being the most common specific adverse events reported. Adverse events that led to study drug discontinuation were experienced by 5% of subjects in the ATRIPLA group and 1% of subjects who stayed on their baseline regimen (SBR group); the majority of subjects who discontinued study drug due to adverse events had switched to ATRIPLA from a prior protease inhibitor-based regimen and the events that led to discontinuation were expected events consistent with the known safety profile of EFV e.g. nervous system symptoms.

Study 934

Study 934 – Treatment Emergent Adverse Events: Assessment of adverse reactions is based on data from Study 934 in which 511 antiretroviral-naïve patients received either FTC+TDF administered in combination with EFV (N=257) or lamivudine/zidovudine administered in combination with EFV (N=254). Adverse events observed in this study were generally consistent with those seen in other studies in treatment experienced or treatment-naïve patients (Table 2). The most common adverse events that occurred in patients receiving EFV+FTC+TDF were mild to moderate dizziness, nausea or diarrhea.

Table 2. 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
Blood and Lymphatic System Disorders		
Anemia	<1%	5%
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%

* National Cancer Institute (NCI) grading system.

Patients who received EFV+FTC+TDF up to 144 weeks in Study 934 reported adverse events similar in nature and severity to those reported in the first 48 weeks of treatment.

Abnormal Hematologic and Clinical Chemistry Findings

Laboratory abnormalities observed in this study were generally consistent with those seen in other studies (Table 3).

Table 3. 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/dL)	15%	17%
Creatine Kinase (M: >990 U/L) (F: >845 U/L)	7%	6%
Serum Amylase (>175U/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 Triglycerides (>750 mg/dL)	4%	2%

* National Cancer Institute (NCI) grading system.

Laboratory abnormalities in patients who received treatment up to 144 weeks in Study 934 were consistent with those observed in the first 48 weeks of treatment.

Through 48 weeks, 7 patients in the EFV+FTC+TDF group and 5 patients in the EFV+lamivudine/zidovudine group experienced a new CDC Class C event (10 and 6 patients, respectively, through 144 weeks). Renal safety assessed by laboratory abnormalities was similar in the two groups and no patient discontinued study drug due to renal events. At Weeks 48 and 144, total limb fat (as measured by dual-energy x-ray absorptiometry) was significantly less in a subgroup of patients in the EFV+lamivudine/zidovudine group compared to the EFV+FTC+TDF subgroup (see Table 4).

Table 4. Study 934 Total Limb Fat at Week 144* (Dual-Energy X-Ray Absorptiometry)

	FTC+TDF+EFV	AZT/3TC+EFV
Week 48[1]	**N=51**	**N=49**
Total Limb Fat (kg) Mean ± S.D (Median)	8.9 ± 5.4 (7.4)	6.9 ± 3.9 (6.0)
Week 144[2]	**N=145**	**N=124**
Total Limb Fat (kg) Mean ± S.D (Median)	9.2 ± 5.4 (7.9)	6.5 ± 4.4 (5.4)
Change from Week 48 to Week 144[3]	**N=48**	**N=38**
Total Limb Fat (kg) Mean ± S.D (Median)	1.1 ± 1.9 (0.9)	-1.1 ± 1.7 (-0.8)

* Baseline data are not available.
[1]P=0.03 for the comparison between arms
[2]P<0.001 for the comparison between arms
[3]P<0.001 for the comparison between arms; P<0.001 for the comparison within arms

Lipids:
In Study 934 at Week 144, the mean increase from baseline fasting triglyceride concentrations was 4 mg/dL for the TDF, FTC and EFV group and 36 mg/dL for the zidovudine/lamivudine and EFV group. For fasting total, LDL, and HDL cholesterol concentrations, the mean increases from baseline were 24 mg/dL, 13 mg/dL, and 10 mg/dL, respectively, for the TDF group and 36 mg/dL, 16 mg/dL, and 12 mg/dL, respectively, for the zidovudine/lamivudine group. The differences between treatment groups reached statistical significance for fasting triglycerides (p=0.047) and fasting total serum cholesterol (p=0.005).

Hepatic Events:
In Study 934, 10 patients treated with EFV, FTC, and TDF and 16 patients treated with EFV and fixed-dose zidovudine/lamivudine were Hepatitis C antibody positive. Among these HCV coinfected patients, one patient (1/10) in the EFV, FTC and TDF arm had elevations in ALT and AST to greater than five times ULN through 144 weeks. One patient (1/16) in the fixed-dose zidovudine/lamivudine arm had elevations in ALT to greater than five times ULN through 144 weeks, and one patient (1/16) in the fixed-dose zidovudine/lamivudine arm had elevations in AST to greater than five times ULN through 144 weeks. Nine patients treated with EFV, FTC and TDF and 4 patients treated with EFV 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 144 weeks. No HBV and/or HCV coinfected patient discontinued from the study due to hepatobiliary disorders (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic** and **Monitoring and Laboratory Tests**).

Study 073

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

In such an open label switch study, subjects may experience an adverse event or laboratory abnormality when they switch to a new treatment compared to subjects who remain on their baseline regimen.

Treatment-emergent AEs such as nervous system symptoms were more frequent in subjects who switched to ATRIPLA than those who stayed on their baseline regimen (SBR group). Such events can be expected in subjects receiving an EFV based regimen for the first time, and are consistent with the known safety profile of EFV.

Table 5. Selected Treatment-Emergent Adverse Events Reported for ≥3% of Subjects in Any Treatment Group in Study 073 (0–48 Weeks)

	FTC+TDF+EFV	SBR
	N=203	N=97
Gastrointestinal Disorder		
Diarrhea	3%	0%
Nausea	3%	2%
Nervous System Disorders		
Somnolence	3%	0%
Dizziness	11%	1%
Psychiatric Disorders		
Insomnia	4%	0%
Abnormal Dreams	7%	0%

Laboratory abnormalities observed in the ATRIPLA group in Study 073 (Table 6) were generally consistent with those in Study 934.

Table 6. Laboratory Abnormalities (≥Grade 3*) Reported in ≥1% of Subjects in Any Treatment Group in Study 073 (0–48 Weeks)

	FTC+TDF+EFV	SBR
	N=203	N=97
Any ≥Grade 3 Laboratory Abnormality	9%	15%
Fasting Cholesterol (>300 mg/dL)	<1%	2%
Serum Amylase (>200 u/L)	3%	2%
AST (M: >180 U/L) (F: >170 U/L)	1%	1%
ALT (M: >215 U/L) (F: >170 U/L)	2%	0%
Hemoglobin (<7.5 g/dL)	0%	1%
Hyperglycemia (>250 mg/dL)	1%	1%
Neutrophil (<750/mm^3)	0%	1%
Fasting Triglycerides (>750 mg/dL)	2%	2%
Total Bilirubin (>3 mg/dL)	0%	7%

* National Cancer Institute (NCI) grading system.

In addition to the adverse events in Study 934 (Table 2) and Study 073 (Table 5), the following adverse events were reported in clinical studies of EFV, FTC, or TDF in combination with other antiretroviral agents. This list is not all inclusive. For additional safety information about Sustiva (EFV), EMTRIVA (FTC) or VIREAD (TDF), consult the Product Monographs for these products.

Efavirenz: The most significant adverse events observed in patients treated with EFV are nervous system symptoms, psychiatric symptoms, and rash **(**see **WARNINGS AND PRECAUTIONS)**. Selected clinical adverse events of moderate or severe intensity reported in ≥2% of EFV-treated patients in three controlled clinical trials included abdominal pain, dyspepsia, anorexia, nausea, vomiting, diarrhea, anxiety, insomnia, dizziness, impaired concentration, nervousness, fatigue, pain, abnormal dreams, headache, depression, rash, somnolence, lipodystrophy, and pruritus.

Other adverse events of moderate or severe intensity reported in <2% of patients in all Phase II/III studies are listed below. Some adverse reactions identified through postmarketing spontaneous reporting are included in this list.

Body as a Whole: alcohol intolerance, allergic reaction, asthenia, fever, hot flushes, influenza-like symptoms, malaise, pain, peripheral edema, syncope, dysregulated body temperature, flank pain, hypersensitivity reactions.

Cardiovascular: arrhythmia, flushing, palpitations, tachycardia, thrombophlebitis, hypertension, congestive heart failure, chest pain

Central and Peripheral Nervous System: ataxia, confusion, convulsions, impaired coordination, migraine headaches, neuralgia, paresthesia, hypoesthesia, peripheral neuropathy, speech disorder, stupor, tremor, neuromuscular paresis, paranoid reaction

Gastrointestinal: dry mouth, pancreatitis, constipation, malabsorption

Liver and Biliary System: hepatic enzymes increased (including ALT, AST and GGT), hepatitis, jaundice, hepatomegaly (see **Post-Market Adverse Drug Reactions**)

Metabolic and Nutritional: hypercholesterolemia, hypertriglyceridemia

Miscellaneous: thrombocytopenia, proteinuria, anemia, pancytopenia, increased sweating

Psychiatric: aggressive reactions, abnormal thinking, aggravated depression, agitation, delusions, amnesia, anxiety, apathy, delirium, depersonalization, emotional lability, euphoria, hallucination, manic reaction, psychosis, neurosis, paranoia, suicide, suicidal ideation, non-fatal suicide attempts, catatonia

Respiratory: asthma, apnea, dyspnea

Skin and Appendages: acne, alopecia, eczema, folliculitis, skin defoliation, urticaria, erythema nodosum, erythema multiforme, Stevens-Johnson syndrome, verruca, nail disorders, skin disorders, photosensitivity reaction

Special Senses: abnormal vision, diplopia, glaucoma, iritis, parosmia, taste perversion, tinnitus

Urinary System: polyuria

For more information, please consult the Sustiva Product Monograph.

Emtricitabine and Tenofovir: Adverse events that occurred in at least 3-5% of patients receiving FTC or TDF with other antiretroviral agents in clinical trials include: anorexia, anxiety, arthralgia, asthenia, increased cough, depressive disorders, dyspepsia, fever, flatulence, myalgia, pain, abdominal pain, back pain, chest pain, paresthesia, peripheral neuropathy (including peripheral neuritis and neuropathy), pneumonia, rhinitis, rash event (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash and allergic reaction), sweating, and weight loss. Skin discoloration has been reported with higher frequency among FTC treated patients. Skin discoloration, manifested by hyperpigmentation on the palms and/or soles was generally mild and asymptomatic and of

little clinical significance. The mechanism is unknown. In addition to the laboratory abnormalities described for Study 934 (Table 3), Grade 3/4 elevations of bilirubin (>2.5 × ULN), pancreatic amylase (>2.0 × ULN), serum glucose (<40 or >250 mg/dL), serum lipase (>2.0 × ULN), and urine glucose (≥3+) occurred in up to 3% of patients treated with FTC or TDF with other antiretroviral agents in clinical trials. For more information, please consult the VIREAD and EMTRIVA Product Monographs.

Post Market Adverse Drug Reactions

In addition to the adverse reaction reports from clinical trials, the following possible adverse reactions have been identified during post-approval use of EFV, FTC, or TDF. Because these events have been reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been considered possible adverse reactions due to a combination of their seriousness, frequency of reporting or potential causal relationship with treatment.

Efavirenz:
Additional adverse experiences* reported in postmarketing surveillance include:

Ear and labyrinth disorders	Vertigo
Endocrine	Gynecomastia
Eye disorders	Blurred vision
Immune system disorders	Immune Reconstitution Inflammatory Syndrome
Musculoskeletal	Rhabdomyolysis
Nervous system disorders	Cerebellar coordination and balance disturbances
Psychiatric	Neurosis
Renal and urinary disorders	Increased CPK
Skin and subcutaneous tissue disorders	Photoallergic dermatitis

Hepatic failure has been reported postmarketing, including some cases in patients with no pre-existing hepatic disease or other identifiable risk factors and also some cases characterized by a fulminant course, sometimes progressing to transplantation or death.

Additional cases of pancreatitis have been reported in postmarketing surveillance. Please see **WARNINGS AND PRECAUTIONS: Hepatic/Biliary/Pancreatitis**.

*Those adverse events not already included under **Clinical Trial Adverse Drug Reactions, Efavirenz**

Emtricitabine:
The following adverse experiences have been reported in post-marketing experience without regard to causality; some events represent a single report.

Blood and lymphatic system disorders:	Thrombocytopenia
Gastrointestinal disorders:	Pancreatitis
General disorders and administrative site conditions:	Pyrexia
Metabolism and nutrition disorders:	Lactic acidosis

Tenofovir disoproxil fumarate:

Immune system disorders:	Allergic reaction (including angioedema)
Metabolism and nutrition disorders:	Lactic acidosis, hypokalemia, hypophosphatemia
Respiratory, thoracic and mediastinal disorders:	Dyspnea
Gastrointestinal disorders:	Pancreatitis, increased amylase, abdominal pain
Hemic and lymphatic system disorders:	Thrombocytopenia
Hepatobiliary disorders:	Hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT, GGT)
Skin and Subcutaneous Tissue Disorders:	Rash
Musculoskeletal and Connective Tissue Disorders:	Rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), muscular weakness, myopathy
Renal and urinary disorders:	Acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria
General disorders and administrative site conditions:	Asthenia

The following adverse reactions, listed under the body system headings above, sometimes appeared to be concurrent with proximal renal tubulopathy: rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), hypokalemia, muscular weakness, myopathy, hypophosphatemia.

There have been three post marketing reports of acute renal failure in patients on concomitant NSAIDS therapy where a relationship to TDF could not be excluded. These events mostly occurred in medically complex patients, where underlying disease processes confound interpretation.

Immune Reconstitution Inflammatory Syndrome

In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy an inflammatory reaction to infectious pathogens (active or inactive) may arise. Autoimmune disorders have also been reported to occur in the setting of immune reconstitution **(**see **WARNINGS and PRECAUTIONS)**.

Exacerbations of Hepatitis after Discontinuation of Treatment

Tenofovir disoproxil fumarate and emtricitabine-containing products: In HIV infected patients coinfected with HBV, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of treatment (see **WARNINGS AND PRECAUTIONS: Special Populations - Patients with HIV and Hepatitis B Virus Coinfection**).

DRUG INTERACTIONS

Drug-Drug Interactions

The drug interactions described in Table 7 are based on studies conducted with either ATRIPLA, the components of ATRIPLA (EFV, FTC or TDF) as individual agents, or are potential drug interactions. This table includes potentially significant interactions, but may not be inclusive of all potential interactions.

Table 7. Established[1] and Other Potentially Significant[2] Drug Interactions:

Concomitant Drug Class: Drug Name	Effect [3]	Clinical Comment
Antiretroviral Agents		
Protease Inhibitor: Atazanavir	↑ tenofovir concentration	Sufficient data are not available to make a dosing recommendation for atazanavir or atazanavir/ritonavir with ATRIPLA. Plasma concentrations of atazanavir were decreased by both EFV and TDF. Atazanavir has been shown to increase tenofovir concentrations. Therefore, the concomitant use of atazanavir and ATRIPLA is not recommended.
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: Indinavir	↓ indinavir concentration	The optimal dose of indinavir, when given in combination with EFV, is not known. Increasing the indinavir dose to 1000 mg every 8 hours does not compensate for the increased indinavir metabolism due to EFV.
Protease Inhibitor: Lopinavir/ritonavir	↓ lopinavir concentration ↑ tenofovir concentration	Insufficient data are available to make a dosing recommendation with ATRIPLA. If used with ATRIPLA, dose adjustment of lopinavir/ritonavir should be considered due to the EFV component (For additional information, consult the Sustiva product monograph). Also, **patients should be monitored for tenofovir-associated adverse events. ATRIPLA should be discontinued in patients who develop tenofovir-associated adverse events.**
CCR5 co-receptor antagonist : Maraviroc	↓ maraviroc	Refer to the full prescribing information for maraviroc for guidance on coadministration with ATRIPLA.

Concomitant Drug Class: Drug Name	Effect [3]	Clinical Comment
Integrase strand transfer inhibitor: Raltegravir	↓ raltegravir	Efavirenz did not have a clinically meaningful effect on the pharmacokinetics of raltegravir.
Protease Inhibitor: Ritonavir	↑ ritonavir concentration ↑ efavirenz concentration	When ritonavir 500 mg every 12 hours was coadministered with EFV 600 mg once daily, the combination was associated with a higher frequency of adverse clinical experiences (eg, dizziness, nausea, paresthesia) and laboratory abnormalities (elevated liver enzymes). Monitoring of liver enzymes is recommended when ATRIPLA is used in combination with ritonavir.
Protease Inhibitor: Saquinavir	↓ saquinavir concentration	Should not be used as sole protease inhibitor in combination with ATRIPLA.
NRTI: Didanosine	↑ didanosine concentration	Higher didanosine concentrations could potentiate didanosine-associated adverse events, including pancreatitis, and neuropathy. **In adults weighing ≥60 kg, the didanosine EC dose should be reduced to 250 mg if coadministered with ATRIPLA. For patients with body weight <60 kg, and creatinine clearance ≥60 mL/min, the recommended dose of ddI-EC is 200 mg. Data are not available to recommend a dose adjustment of didanosine for patients with creatinine clearance <60mL/min. Coadministration of ATRIPLA and didanosine EC 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.**
HCV Antiviral Agents		
NS5A inhibitor /NS3/4A protease inhibitor: Elbasvir/grazoprevir	↓ elbasvir ↓ grazoprevir	Coadministration of efavirenz with elbasvir/grazoprevir reduced elbasvir AUC and Cmax by 54% and 45%, respectively, and reduced grazoprevir AUC and Cmax by 83% and 87%, respectively, compared to elbasvir/grazoprevir alone. Concomitant administration of ATRIPLA with elbasvir/grazoprevir is contraindicated [see CONTRAINDICATIONS] because it may lead to loss of virologic response to elbasvir/grazoprevir. This loss is due to significant decreases in elbasvir and grazoprevir plasma concentrations caused by CYP3A4 induction. For additional information, please consult the Zepatier® (elbasvir/grazoprevir) prescribing information.

Concomitant Drug Class: Drug Name	Effect [3]	Clinical Comment
NS5A inhibitor/NS5B polymerase inhibitor: Ledipasvir/sofosbuvir	↑ tenofovir	Concomitant administration of HARVONI (ledipasvir/sofosbuvir) with ATRIPLA resulted in increases in tenofovir (AUC ↑ 98%, C_{max} ↑ 79% and C_{min} ↑163%), compared with ATRIPLA alone. No dose adjustment of ATRIPLA or HARVONI is required. Patients receiving ATRIPLA with HARVONI should be monitored for adverse reactions associated with TDF.
NS5B polymerase inhibitor/NS5A inhibitor: Sofosbuvir/velpatasvir	↑ tenofovir ↓ velpatasvir	Concomitant administration of EPCLUSA (sofosbuvir/velpatasvir) with ATRIPLA increased tenofovir AUC, C_{max}, and C_{min} by 81%, 77%, and 121%, respectively, compared with ATRIPLA alone, and decreased velpatasvir AUC, C_{max}, and C_{min} by 53%, 47%, and 57%, respectively, compared with EPCLUSA alone. Coadministration of ATRIPLA with EPCLUSA is not recommended.
NS5B polymerase inhibitor/NS5A inhibitor/NS3/4A inhibitor: Sofosbuvir/velpatasvir/ voxilaprevir	↑ tenofovir[5] ↓ velpatasvir[5] ↓ voxilaprevir[5]	Concomitant administration of EFV with a HCV treatment containing velpatasvir has been shown to decrease velpatasvir exposure. Tenofovir exposure is expected to increase and velpatasvir and voxilaprevir are expected to decrease upon concomitant administration of ATRIPLA and VOSEVI (sofosbuvir/velpatasvir/voxilaprevir). Coadministration of ATRIPLA with VOSEVI is not recommended.
NS5B polymerase inhibitor: Sofosbuvir	↑ tenofovir	Concomitant administration of SOVALDI (sofosbuvir) with ATRIPLA resulted in an increase in tenofovir C_{max} by 25%, compared with ATRIPLA alone. Tenofovir AUC and C_{min} were unaltered by sofosbuvir coadministration. No dose adjustment of ATRIPLA or SOVALDI is required.
Protease inhibitor: Simeprevir	↓ simeprevir[1] ↔ efavirenz[1]	Concomitant use of simeprevir with EFV resulted in significantly decreased plasma concentrations of simeprevir (AUC ↓ 71%, C_{max} ↓ 51%, C_{min} ↓ 91%) due to CYP3A induction by EFV. This may result in loss of therapeutic effect of simeprevir. It is not recommended to co-administer simeprevir with ATRIPLA. Alternatives should be considered. Refer to the prescribing information for simeprevir for more information.

Concomitant Drug Class: Drug Name	Effect [3]	Clinical Comment
Other Agents		
Anticoagulant: Warfarin	↑ or ↓ warfarin concentration	Plasma concentrations and effects potentially increased or decreased by EFV.
Acenocoumarol	↑ or ↓ acenocoumarol concentration	It is recommended that INR be monitored.
Anticonvulsants: Carbamazepine	↓ carbamazepine concentration ↓ efavirenz concentration	Periodic monitoring of carbamazepine plasma levels should be conducted. There are insufficient data to make a dose recommendation for ATRIPLA. Alternative anticonvulsant treatment should be considered.
Anticonvulsants: Phenytoin Phenobarbital	↓ anticonvulsant concentration ↓ efavirenz concentration	Potential for reduction in anticonvulsant and/or EFV plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.
Antidepressants: Bupropion	↓ bupropion concentration	The effect of EFV on buproprion exposure is thought to be due to the induction of bupropion metabolism. Bupropion dose adjustments should be guided by clinical response, but the maximum recommended dose of bupropion should not be exceeded. No dose adjustment is necessary for EFV.
Sertraline	↓ sertraline concentration	It may be necessary to retitrate the sertraline dose to achieve the desired clinical effect. In a drug interaction study in healthy subjects, an increased incidence of impaired concentration was seen in subjects receiving sertraline concomitantly with EFV.
Antifungals:		See CONTRAINDICATIONS for other antifungals.
Itraconazole	↓ itraconazole concentration ↓ hydroxy-itraconazole concentration	Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered.
Posaconazole	↓ posaconazole	Avoid concomitant use of posaconazole and ATRIPLA unless the benefit to the patient outweighs the risk.
Ketoconazole	↓ ketoconazole concentration	Drug interaction studies with ATRIPLA and ketoconazole have not been conducted. Efavirenz has the potential to decrease plasma concentrations of ketoconazole.

Concomitant Drug Class: Drug Name	Effect [3]	Clinical Comment
Anti-infective: Clarithromycin	↓ clarithromycin concentration ↑ 14-OH metabolite concentration	Consider alternatives to macrolide antibiotics because of the risk of QT interval prolongation. Clinical significance unknown. In uninfected volunteers, 46% developed rash while receiving EFV and clarithromycin. No dose adjustment of ATRIPLA is recommended when given with clarithromycin. Alternatives to clarithromycin, such as azithromycin, should be considered. Not all macrolide antibiotics have been studied in combination with EFV.
Antimalarial: Artemether/lumefantrine[4]	↓ artemether ↓ dihydroartemisinin ↓ lumefantrine	Consider alternatives to artemether/lumefantrine because of the risk of QT interval prolongation. Coadministration of EFV with artemether/ lumefantrine resulted in a decrease in exposures to artemether, dihydroartemisinin (active metabolite of artemether), and lumefantrine. Exposure to EFV was not significantly affected. Since decreased concentrations of artemether, dihydroartemisinin, or lumefantrine may result in a decrease of antimalarial efficacy, caution is recommended when ATRIPLA and artemether/lumefantrine tablets are coadministered.
Antimalarial: Atovaquone/Proguanil	↓ atovaquone ↓ proguanil	Coadministration of EFV with atovaquone/proguanil resulted in a decrease in exposures to atovaquone and proguanil. Since decreased concentrations of atovaquone and proguanil may result in a decrease of antimalarial efficacy, concomitant administration should be avoided whenever possible.
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	An additional 200 mg/day (800 mg total) of EFV is recommended when ATRIPLA is administered with rifampin in adult patients weighing 50 kg or more.

Concomitant Drug Class: Drug Name	Effect [3]	Clinical Comment
Calcium Channel Blockers: Diltiazem	↓ diltiazem ↓ desacetyl diltiazem ↓ N-mono desmethyl diltiazem	Diltiazem levels are markedly decreased when coadministered with EFV. Efavirenz levels decreased to a lesser extent (see Table 9 and Table 10). Patients should be closely monitored for possible decreased diltiazem effects and increased adverse events and laboratory abnormalities associated with EFV. Refer to the prescribing information for diltiazem for guidance on dose adjustment.
Others (e.g. felodipine, nifedipine, verapamil)	↓ calcium channel blocker	No data are available on the potential interactions of EFV 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 prescribing information for the calcium channel blocker).
Immunosuppressants: cyclosporine, tacrolimus, sirolimus	↓ cyclosporine, tacrolimus, sirolimus concentration	When an immunosuppressant metabolized by CYP3A4 is administered with EFV, decreased exposure of the immunosuppressant may be expected due to CYP3A4 induction. Immunosuppressants metabolized by CYP3A4 are not anticipated to affect exposure of EFV. There were no clinically significant pharmacokinetic interactions when FTC/TDF was coadministered with tacrolimus. Dose adjustments of the immunosuppressant may be required when used with ATRIPLA. Close monitoring of immunosuppressant concentrations for at least 2 weeks (until stable concentrations are reached) is recommended when starting or stopping treatment with ATRIPLA.
HMG-CoA Reductase inhibitors: Atorvastatin Pravastatin Simvastatin	↓ atorvastatin concentration ↓ pravastatin concentration ↓ simvastatin concentration	Plasma concentrations of atorvastatin, pravastatin, and simvastatin decreased with EFV. Consult the complete prescribing information for the HMG-CoA reductase inhibitor for guidance on individualizing the dose.

Concomitant Drug Class: Drug Name	Effect [3]	Clinical Comment
Hormonal contraceptive:		A reliable method of barrier contraception must be used in addition to hormonal contraceptives.
Oral: Ethinyl estradiol/ Norgestimate	↓ active metabolites of norgestimate	Efavirenz had no effect on ethinyl estradiol concentrations, but progestin levels (norelgestromin and levonorgestrel) were markedly decreased. The clinical significance of these effects is not known. No effect of ethinyl estradiol/norgestimate on EFV plasma concentrations was observed.
Implant: Etonogestrel	↓ etonogestrel	The interaction between etonogestrel and EFV has not been studied. Decreased exposure of etonogestrel may be expected (CYP3A4 induction), and there have been occasional postmarketing reports of contraceptive failure with etonogestrel in EFV-exposed patients.
Narcotic Analgesic: Methadone	↓ methadone concentration	Coadministration of EFV in HIV-infected individuals with a history of injection drug use resulted in decreased plasma levels of methadone and signs of opiate withdrawal. Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.

1. See Table 8-Table 11.
2. This table is not all inclusive.
3. Increase = ↑; Decrease = ↓; ↔ = No Effect
4. Not marketed in Canada.
5. A study with VOSEVI (sofosbuvir/velpatasvir/voxilaprevir) was not conducted. The interactions shown are expected based on an interaction study with EPCLUSA (sofosbuvir/velpatasvir).

Efavirenz:

Efavirenz has been shown in vivo to cause hepatic enzyme induction, thus increasing the biotransformation of some drugs metabolized by CYP3A4 and CYP2B6. In vitro studies have demonstrated that EFV inhibits 2C9, 2C19 and 3A4 isozymes in the range of observed EFV plasma concentrations. Coadministration of EFV with drugs primarily metabolized by these isozymes may result in altered plasma concentrations of the coadministered drug. Therefore, appropriate dose adjustments may be necessary for these drugs.

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

There is limited information available on the potential for a pharmacodynamic interaction between EFV and drugs that prolong the QTc interval. QTc prolongation has been observed with the use of EFV (see **ACTION AND CLINICAL PHARMACOLOGY**). Consider alternatives to ATRIPLA when coadministered with a drug with a known risk of Torsade de Pointes.

Drug interaction studies were performed with EFV and other drugs likely to be coadministered or drugs commonly used as probes for pharmacokinetic interaction. There was no clinically significant interaction observed between EFV and zidovudine, lamivudine,

azithromycin, fluconazole, lorazepam, cetirizine, paroxetine or sofosbuvir. Single doses of famotidine or an aluminum and magnesium antacid with simethicone had no effects on EFV exposures. The effects of coadministration of EFV on C_{max} and AUC are summarized in Table 8 (effect of other drugs on EFV) and Table 9 (effect of EFV on other drugs)(see **CONTRAINDICATIONS**).

Specific drug interaction studies have not been performed with EFV and NRTIs other than lamivudine, zidovudine and TDF. The steady-state pharmacokinetics of EFV and tenofovir were unaffected when EFV and TDF were administered together versus each agent dosed alone. Clinically significant interactions would not be expected since the NRTIs are metabolized via a different route than EFV and would be unlikely to compete for the same metabolic enzymes and elimination pathways.

Table 8. Drug Interactions: Changes in Pharmacokinetic Parameters for EFV in the Presence of the Coadministered Drug

Coadministered Drug	Dose of Coadministered Drug	EFV Dose	N	Mean % Change of EFV Pharmacokinetic Parameters[1]		
				C_{max}	AUC	C_{min}
Atazanavir[4]	400 mg qd x 20 days	600 mg qd d 7-20	--	↔	↔	NA
Indinavir	800 mg q8h × 14 days	200 mg × 14 days	11	↔	↔	↔
Ledipasvir/ Sofosbuvir	90/400 mg qd x 10 days	600 mg qd x 10 days	15	↔	↔	↔
Sofosbuvir/ Velpatasvir	400/100 mg qd	600 mg qd	15	↔	↔	↔
Sofosbuvir	400 mg qd x 10 days	600 mg qd x 10 days	16	↔	↔	↔
Lopinavir/ Ritonavir	400/100 mg q12h × 9 days	600 mg × 9 days	11, 12[3]	↔	↓ 16	↓ 16
Nelfinavir	750 mg q8h × 7 days	600 mg × 7 days	10	↓ 12	↓ 12	↓ 21
Ritonavir	500 mg q12h × 8 days	600 mg × 10 days	9	↑ 14	↑ 21	↑ 25
Saquinavir SGC[2]	1200 mg q8h × 10 days	600 mg × 10 days	13	↓ 13	↓ 12	↓ 14
Tenofovir disoproxil fumarate	300 mg qd	600 mg x 14 days	30	↔	↔	↔
Simeprevir	150 mg daily for 14 days	600 mg x 14 days	23	↔	↔	↔

Coadministered Drug	Dose of Coadministered Drug	EFV Dose	N	Mean % Change of EFV Pharmacokinetic Parameters[1]		
				C_{max}	AUC	C_{min}
Clarithromycin	500 mg q12h × 7 days	400 mg × 7 days	12	↑ 11	↔	↔
Azithromycin	600 mg single dose	400 mg x 7 days	14	↔	↔	↔
Rifabutin	300 mg qd × 14 days	600 mg × 14 days	11	↔	↔	↓ 12
Rifampin	600 mg × 7 days	600 mg × 7 days	12	↓ 20	↓ 26	↓ 32
Antacid: Aluminum hydroxide 400 mg Magnesium hydroxide 400 mg + simethicone 30 mg	30 mL single dose	400 mg single dose	17	↔	↔	NA
Carbamazepine	200 mg qd × 3 days, 200 mg BID × 3 days, then 400 mg qd × 15 days	600 mg × 35 days	14	↓ 21	↓ 36	↓ 47
Paroxetine	20 mg qd × 14 days	600 mg × 14 days	12	↔	↔	↔
Sertraline	50 mg qd × 14 days	600 mg × 14 days	13	↑ 11	↔	↔
Fluconazole	200 mg x 7 days	400 mg x 7 days	10	↔	↑ 16	↑ 22
Itraconazole	200 mg q 12h x 14 days	600 mg x 28 days	16	↔	↔	↔
Voriconazole	400 mg po q12h × 1 day then 200 mg po q12h × 8 days	400 mg × 9 days	—	↑ 38	↑ 44	NA
	300 mg po q12h days 2-7	300 mg × 7 days	—	↓14[5]	↔[5]	NA
	400 mg po q12h days 2-7	300 mg × 7 days	—	↔[5]	↑17[5]	NA

Coadministered Drug	Dose of Coadministered Drug	EFV Dose	N	Mean % Change of EFV Pharmacokinetic Parameters[1]		
				C_{max}	AUC	C_{min}
Diltiazem	240 mg x 14 days	600 mg x 28 days	12	↑ 16	↑ 11	↑ 13
Cetirizine	10 mg single dose	600 mg x 10 days	11	↔	↔	↔
Famotidine	40 mg single dose	400 mg single dose	17	↔	↔	NA
Atorvastatin	10 mg qd x 4 days	600 mg x 15 days	14	↔	↔	↔
Pravastatin	40 mg qd x 4 days	600 mg x 15 days	11	↔	↔	↔
Simvastatin	40 mg qd x 4 days	600 mg x 15 days	14	↓ 12	↔	↓ 12

1. Increase = ↑; Decrease = ↓; No Effect = ↔
2. Soft Gelatin Capsule.
3. Parallel-group design; N for EFV+lopinavir/ritonavir, N for EFV alone.
4. Comparison with historical data suggests that Atazanavir does not affect EFV PK.
5. Relative to steady-state administration of EFV (600 mg once daily for 9 days).

Table 9. Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of EFV

Coadministered Drug	Dose of Coadministered Drug	EFV Dose	N	Mean % Change of Coadministered Drug Pharmacokinetic Parameters[1]		
				C_{max}	AUC	C_{min}
Atazanavir	400 mg qd with a light meal d 1–20	600 mg qd with a light meal d 7–20	27	↓ 59	↓ 74	↓ 93
	400 mg qd d 1–6, then 300 mg qd d 7–20 with ritonavir 100 mg qd and a light meal	600 mg qd 2 h after atazanavir and ritonavir d 7–20	13	↑ 14[3]	↑ 39[3]	↑ 48[3]
	300 mg qd/ritonavir 100 mg qd d 1-10 (pm), then 400 mg qd/ritonavir 100 mg qd d 11-24 (pm) (simultaneous with EFV)	600 mg qd d 11-24 (pm)	14	↑ 17	↔	↓ 42
Indinavir	1000 mg q8h × 10 days	600 mg × 10 days	20			
	After morning dose			↔[4]	↓ 33[4]	↓ 39[4]
	After afternoon dose			↔[4]	↓ 37[4]	↓ 52[4]
	After evening dose			↓ 29[4]	↓ 46[4]	↓ 57[4]
Indinavir/Ritonavir	Indinavir 800 mg + ritonavir 100 mg q12 hr d 1–29	600 mg d 15-29		↓ 17[5]	↓ 25[5]	↓ 50[5]
Ledipasvir/ Sofosbuvir	90/400 mg qd x 10 days	600 mg qd x 10 days	15	↓ 34	↓ 34	↓ 34
Ledipasvir						
Sofosbuvir				↔	↔	NA
GS-331007[10]				↔	↔	↔
Sofosbuvir	400/100 mg qd	600 mg qd	14	↑ 38	↔	NA
GS-331007[10]				↔	↔	↔
Velpatasvir				↓ 47	↓ 53	↓ 57
Sofosbuvir	400 mg qd x 10 days	600 mg qd x10 days	16	↓ 19	↔	NA
GS-331007[10]				↓ 23	↔	NA

Coadministered Drug	Dose of Coadministered Drug	EFV Dose	N	Mean % Change of Coadministered Drug Pharmacokinetic Parameters[1]		
				C_{max}	AUC	C_{min}
Lopinavir/ Ritonavir	400/100 mg (capsule*) q12h × 9 days	600 mg × 9 days	11, 7[6]	↔[7]	↓ 19[7]	↓ 39[7]
	600/150 mg (tablet) q12h × 10 days with EFV compared to 400/100 mg q12h alone	600 mg × 9 days	23	↑ 36	↑ 36	↑ 32
Raltegravir	400 mg single dose	600 mg	9	↓ 36	↓ 36	↓ 21
Nelfinavir	750 mg q8h × 7 days	600 mg × 7 days	10	↑ 21	↑ 20	↔
Metabolite AG-1402				↓ 40	↓ 37	↓ 43
Ritonavir	500 mg q12h × 8 days	600 mg × 10 days	11			
	After AM dose			↑ 24	↑ 18	↑ 42
	After PM dose			↔	↔	↑ 24
Saquinavir SGC[9]	1200 mg q8h × 10 days	600 mg × 10 days	12	↓ 50	↓ 62	↓ 56
Lamivudine	150 mg q 12 h x 14 days	600 mg × 14 days	9	↔	↔	↑ 265
Zidovudine	300 mg q 12 h x 14 days	600 mg × 14 days	9	↔	↔	↑ 225
Tenofovir disoproxil fumarate	300 mg qd	600 mg × 14 days	29	↔	↔	↔
Simeprevir	150 mg daily for 14 days	600 mg x 14 days	23	↓ 51	↓ 71	↓ 91
Maraviroc	100 mg bid	600 mg qd	12	↓ 51	↓ 45	↓ 45
Clarithromycin	500 mg q12h × 7 days	400 mg × 7 days	11	↓ 26	↓ 39	↓ 53
14-OH Metabolite				↑ 49	↑ 34	↑ 26
Artemether*	80/480 mg bid x 3 days before and during EFV coadministration	600 mg x 26 days	12	↓ 21	↓ 51	NA
Dihydroartemisinin (active metabolite of artemether)*				↓ 38	↓ 46	NA
Lumefantrine*				↔	↓ 21	NA

Coadministered Drug	Dose of Coadministered Drug	EFV Dose	N	Mean % Change of Coadministered Drug Pharmacokinetic Parameters[1]		
				C_{max}	AUC	C_{min}
Azithromycin	600 mg single dose	400 mg x 7 days	14	↑ 22	↔	NA
Rifabutin 25-0-desacetylrifabutin	300 mg qd × 14 days	600 mg × 14 days		↓ 32 ↓ 49[2]	↓ 38 ↓ 74[2]	↓ 45 NA
Carbamazepine Epoxide Metabolite	200 mg qd × 3days, 200 mg BID × 3 days, then 400 mg qd × 29 days	600 mg × 14 days	12	↓ 20 ↔	↓ 27 ↔	↓ 35 ↓ 13
Bupropion Hydroxybupropion	150 mg single dose (sustained-release)	600 mg x 14 days	13	↓ 34 ↑ 50	↓ 55 ↔	NA NA
Paroxetine	20 mg daily x 14 days	600 mg x 14 days	16	↔	↔	↔
Oral contraceptive: Ethinyl estradiol/ Norgestimate Ethinyl estradiol Norelgestromin Levonorgestrel	0.035 mg/ 0.25 mg x 14 days	600 mg x 14 days	 21 21 6	 ↔ ↓ 46 ↓ 80	 ↔ ↓ 64 ↓ 83	 ↔ ↓ 82 ↓ 86
Methadone	Stable maintenance 35–100 mg daily	600 mg 14-21 days	11	↓ 45	↓ 52	NA
Sertraline N desmethyl sertraline	50 mg qd × 14 days	600 mg × 14 days	13	↓ 29 ↓17	↓ 39 ↓20	↓ 46 ↓20
Fluconazole	200 mg x 7 days	400 mg x 7 days	10	↔	↔	↔
Itraconazole Hydro-intraconazole	200 mg q12h x 28 days	600 mg x 14 days	18	↓37 ↓35	↓39 ↓37	↓44 ↓43
Posaconazole	400 mg (oral suspension) bid x 10 and 20 days	400 mg x 10 and 20 days		↓45	↓50	NA
Voriconazole	400 mg po q12h × 1 day then 200 mg po q12h x 8 days	400 mg × 9 days	—	↓ 61	↓ 77	NA

Coadministered Drug	Dose of Coadministered Drug	EFV Dose	N	Mean % Change of Coadministered Drug Pharmacokinetic Parameters[1]		
				C_{max}	AUC	C_{min}
	300 mg po q12h days 2-7	300 mg × 7 days	—	↓36[8]	↓55[8]	NA
	400 mg po q12h days 2-7	300 mg × 7 days	—	↑23[8]	↔[8]	NA
Lorazepam	2 mg single dose	600 mg x 10 days	12	↑ 16	↔	NA
Diltiazem	240 mg x 21 days	600 mg x 14 days	13	↓60	↓69	↓ 63
Desacetyl diltiazem				↓64	↓75	↓ 62
N-monodesmethyl diltiazem				↓28	↓37	↓ 37
Cetirizine	10 mg single dose	600 mg x 10 days	11	↓24	↔	NA
Atorvastatin	10 mg qd × 4 days	600 mg × 15 days	14	↓ 14	↓ 43	↓ 69
Total active (including metabolites				↓ 15	↓ 32	↓ 48
Pravastatin	40 mg qd × 4 days	600 mg × 15 days	13	↓ 32	↓ 44	↓ 19
Simvastatin	40 mg qd × 4 days	600 mg × 15 days	14	↓ 72	↓ 68	↓ 45
Total active (including metabolites				↓ 68	↓ 60	NA

1. Increase = ↑; Decrease = ↓; No Effect = ↔.
2. Based on arithmetic means.
3. Compared with atazanavir 400 mg qd alone.
4. Comparator dose of indinavir was 800 mg q8h × 10 days.
5. Compared to indinavir 800 twice daily given with ritonavir 100 mg twice daily without EFV. The geometric Cmin for indinavir (0.33 mg/L) when given with ritonavir and EFV was higher than the mean historical Cmin (0.15 mg/L) when indinavir was given alone at 800 mg every 8 hours. When EFV 600 mg once daily was given with indinavir/ritonavir 800/100 mg twice daily in HIV-1-infected patients (n=6), the pharmacokinetics of indinavir and EFV were generally comparable to these data from uninfected volunteers.
6. Parallel-group design; N for EFV+lopinavir/ritonavir, N for lopinavir/ritonavir alone.
7. Values are for lopinavir. The pharmacokinetics of ritonavir 100 mg q12h are unaffected by concurrent EFV.
8. Relative to steady-state administration of voriconazole (400 mg for 1 day, then 200 mg po q12h for 2 days).
9. Soft Gelatin Capsule.
10. The predominant circulating nucleoside metabolite of sofosbuvir.

* Not marketed in Canada.

Emtricitabine and tenofovir disoproxil fumarate:
The steady state pharmacokinetics of FTC and tenofovir were unaffected when FTC and TDF were administered together versus each agent dosed alone.

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

Emtricitabine and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. No drug-drug interactions due to competition for renal excretion have been observed. Since FTC and tenofovir are primarily eliminated by the kidneys, coadministration of ATRIPLA with drugs that reduce renal function (see **WARNINGS AND PRECAUTIONS: Renal)** or compete for active tubular secretion may increase serum concentrations of FTC, tenofovir, and/or other renally eliminated drugs. Some examples of drugs that compete for active tubular secretion include, but are not limited to cidofovir, acyclovir, valacyclovir, ganciclovir, and valganciclovir.

ATRIPLA should not be administered with HEPSERA (adefovir dipivoxil).

No clinically significant drug interactions have been observed between FTC and famciclovir, indinavir, zidovudine, stavudine, and TDF. Similarly, no clinically significant drug interactions have been observed between TDF and abacavir, ribavirin, EFV, FTC, entecavir, indinavir, lamivudine, lopinavir/ritonavir, methadone, oral contraceptives, nelfinavir, sofosbuvir or saquinavir/ritonavir in studies conducted in healthy volunteers.

Atazanavir and lopinavir/ritonavir have been shown to increase tenofovir concentrations (see clinical comments in Table 7). The mechanism of this interaction is unknown. The effects of coadministration of tenofovir on $C_{max,}$ C_{min} and AUC are summarized in Table 10 (effect of other drugs on tenofovir) and Table 11 (effect of tenofovir on other drugs).

Table 10. Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir in the Presence of the Coadministered Drug[1,2]

Coadministered Drug	Dose of Coadministered Drug (mg)	N	Mean % Change of Tenofovir Pharmacokinetic Parameters[3] (90% CI)		
			C_{max}	AUC	C_{min}
Atazanavir[4]	400 once daily × 14 days	33	↑ 14 (↑ 8 to ↑ 20)	↑ 24 (↑ 21 to ↑ 28)	↑ 22 (↑ 15 to ↑ 30)
Didanosine (enteric-coated)	400 once	25	↔	↔	↔
Didanosine (buffered)	250 or 400 once daily × 7 days	14	↔	↔	↔
Entecavir	1 mg once daily × 10 days	28	↔	↔	↔
Ledipasvir/ Sofosbuvir	90/400 once daily	15	↑ 79	↑ 98	↑ 163
Sofosbuvir/ Velpatasvir	400/100 once daily	15	↑ 77 (↑ 53 to ↑ 104)	↑ 81 (↑ 68 to ↑ 94)	↑ 121 (↑ 100 to ↑ 143)
Lopinavir/Ritonavir	400/100 twice daily × 14 days	24	↔	↑ 32 (↑ 25 to ↑ 38)	↑ 51 (↑ 37 to ↑ 66)
Sofosbuvir	400 once daily	16	↑ 25	↔	↔

1. All interaction studies conducted in healthy volunteers.
2. Patients received TDF 300 mg once daily.
3. Increase = ↑; Decrease = ↓; No Effect = ↔
4. Reyataz Product Monograph.

Table 11. Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Tenofovir [1,2]

Coadministered Drug	Dose of Coadministered Drug (mg)	N	Mean % Change of Coadministered Drug Pharmacokinetic Parameters[3] (90% CI)		
			C_{max}	AUC	C_{min}
Atazanavir[4]	400 once daily × 14 days	34	↓ 21 (↓ 27 to ↓ 14)	↓ 25 (↓ 30 to ↓ 19)	↓ 40 (↓ 48 to ↓ 32)
	Atazanavir/ritonavir 300/100 once daily × 42 days	10	↓ 28 (↓ 50 to ↑ 5)	↓ 25[5] (↓ 42 to ↓ 3)	↓ 23[5] (↓ 46 to ↑ 10)
Entecavir	1 mg once daily × 10 days	28	↔	↑ 13 (↑ 11 to ↑ 15)	↔
Lopinavir	Lopinavir/ritonavir 400/100 twice daily × 14 days	24	↔	↔	↔
Ritonavir	Lopinavir/ritonavir 400/100 twice daily × 14 days	24	↔	↔	↔
Sofosbuvir	Sofosbuvir 400 once daily x 10 days	16	↓ 19	↔	NA
GS-331007[6]			↓ 23	↔	NA

1. All interaction studies conducted in healthy volunteers.
2. Patients received TDF 300 mg once daily.
3. Increase = ↑; Decrease = ↓; No Effect = ↔
4. Reyataz Product Monograph.
5. In HIV-infected patients, addition of TDF to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and C_{min} values of atazanavir that were 2.3- and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone.
6. The predominant circulating nucleoside metabolite of sofosbuvir.

Coadministration of TDF with didanosine results in changes in the pharmacokinetics of didanosine that may be of clinical significance. Table 12 summarizes the effects of TDF on the pharmacokinetics of didanosine. Concomitant dosing of TDF with didanosine buffered tablets or enteric-coated capsules significantly increased the C_{max} and AUC of didanosine. When didanosine 250 mg enteric-coated capsules were administered with TDF, systemic exposures of didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions. The mechanism of this interaction is unknown. **Increases in didanosine concentrations of this magnitude could potentiate didanosine-associated adverse events, including pancreatitis, lactic acidosis, and neuropathy.** In addition,

suppression of CD4+ counts has been observed in patients receiving TDF with didanosine at a dose of 400 mg daily.

Therefore, the recommended dose of didanosine EC is 250 mg for HIV infected adults with body weight ≥60 kg and creatinine clearance ≥60 mL/min when coadministered with ATRIPLA. For patients with body weight <60 kg, and creatinine clearance ≥60 mL/min, the recommended dose of ddI-EC is 200 mg. Data are not available to recommend a dose adjustment of didanosine for patients with creatinine clearance <60mL/min (for didanosine EC dosing adjustment recommendations, see Table 8). **Coadministration of ATRIPLA and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse events.**

Caution should be used when coadministering reduced-dose didanosine, tenofovir, and an NNRTI in treatment-naïve patients with high viral loads at baseline since such use has been associated with reports of a high rate of virologic failure and emergence of resistance at an early stage. All patients receiving TDF and didanosine concomitantly should be closely monitored for didanosine-related adverse events and clinical response.

Table 12. Drug Interactions: Changes in Pharmacokinetic Parameters for Didanosine in the Presence of TDF[1,2]

Didanosine Dose (mg)/Method of Administration[4]	TDF Method of Administration[2,4]	N	Mean % Change (90% CI) vs. Didanosine 400 mg Alone, Fasted[3]	
			C_{max}	AUC
Buffered Tablets				
400 once daily[5] × 7 days	Fasted 1 hour after didanosine	14	↑ 28 (↑ 11 to ↑ 48)	↑ 44 (↑ 31 to ↑ 59)
Enteric coated Capsules				
400 Once, Fasted	With food, 2 hr after didanosine	26	↑ 48 (↑ 25 to ↑ 76)	↑ 48 (↑ 31 to ↑ 67)
400 Once, with Food	Simultaneously with didanosine	26	↑ 64 (↑ 41 to ↑ 89)	↑ 60 (↑ 44 to ↑ 79)
250 Once, Fasted	With food, 2 hr after didanosine	28	↓ 10 (↓ 22 to ↑ 3)	↔
250 Once, Fasted	Simultaneously with didanosine	28	↔	↑ 14 (0 to ↑ 31)
250 Once, with Food	Simultaneously with didanosine	28	↓ 29 (↓ 39 to ↓ 18)	↓ 11 (↓ 23 to ↑ 2)

1. All interaction studies conducted in healthy volunteers.
2. Patients received TDF 300 mg once daily.
3. Increase = ↑; Decrease = ↓; No Effect = ↔
4. Administration with food was with a light meal (~373 kcal, 20% fat).
5 Includes 4 subjects weighing <60 kg receiving ddI 250 mg.

Drug-Food Interactions

Interactions of ATRIPLA with food have not been established. In studies of the individual components of ATRIPLA, increased EFV and tenofovir concentrations were observed following administration with food (see **ACTION AND CLINICAL PHARMACOLOGY, Effect of Food on Oral Absorption**). Increased concentrations of EFV may lead to an increase in frequency of adverse events.

Drug-Herb Interactions

Interactions of ATRIPLA with herbs have not been established. Concomitant use of St. John's wort (*Hypericum perforatum*) or St. John's wort-containing products with ATRIPLA is contraindicated (see **CONTRAINDICATIONS**). Coadministration of NNRTIs, including EFV, with St. John's wort is expected to substantially decrease NNRTI concentrations. Decreased concentrations may result in suboptimal levels of EFV and lead to loss of virologic response and possible resistance to EFV or to the class of NNRTIs.

Drug-Laboratory Interactions

Interactions of ATRIPLA with laboratory tests have not been established.

Efavirenz Assay Interference

Cannabinoid Test Interaction: Efavirenz does not bind to cannabinoid receptors. False-positive urine cannabinoid test results have been reported with some screening assays in uninfected and HIV-infected subjects receiving EFV. Confirmation of positive screening tests for cannabinoids by a more specific method such as gas chromatography/mass spectrometry is recommended. For more information, please consult the Sustiva Product Monograph.

DOSAGE AND ADMINISTRATION

The recommended dose of ATRIPLA is one tablet of 600 mg/ 200 mg/ 300 mg EFV/FTC/TDF, once daily, taken orally on an empty stomach. Dosing at bedtime may improve the tolerability of nervous system symptoms (see **WARNINGS AND PRECAUTIONS, Neurologic** and **INFORMATION FOR THE CONSUMER**).

Dose Adjustment for Renal Impairment

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

Dose Adjustment for Hepatic Impairment

ATRIPLA is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) because of insufficient data. Caution should be exercised in

administering ATRIPLA to patients with mild hepatic impairment because of the extensive cytochrome P450-mediated metabolism of EFV and limited clinical experience. (see **WARNINGS AND PRECAUTIONS: Hepatic Impairment**, **Monitoring and Laboratory Tests** and **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacokinetics: Special Populations and Conditions**).

Missed Dose

If a patient misses a dose at the regularly scheduled time, but then remembers it that same day, the patient should take the missed dose immediately. The patient should not take more than 1 dose of ATRIPLA in a day.

OVERDOSAGE

For management of a suspected drug overdose, please contact your regional Poison Control Centre.

If overdose occurs the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary including monitoring of vital signs and observation of the patient's clinical status. Administration of activated charcoal may be used to aid removal of EFV. Hemodialysis can remove both FTC and TDF (refer to information below), but, since EFV is highly protein bound, dialysis is unlikely to significantly remove the drug from blood. There is no specific antidote for overdose with EFV.

Efavirenz:
Some patients accidentally taking 600 mg twice daily have reported increased nervous system symptoms. One patient experienced involuntary muscle contractions and a second patient experienced vomiting after taking twice the recommended dose.

Emtricitabine:
Limited clinical experience is available at doses higher than the therapeutic dose of EMTRIVA. In one clinical pharmacology study single doses of FTC 1200 mg were administered to 11 patients. No severe adverse reactions were reported. The effects of higher doses are not known.

Hemodialysis treatment removes approximately 30% of the FTC dose over a 3-hour dialysis period starting within 1.5 hours of FTC dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min), however, a single treatment does not significantly affect FTC C_{max} or AUC. It is not known whether FTC can be removed by peritoneal dialysis.

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

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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

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

Tenofovir disoproxil fumarate:
Tenofovir disoproxil fumarate is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir disoproxil fumarate 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.

Pharmacodynamics

Antiviral Activity In Vitro:
Efavirenz, emtricitabine and tenofovir disoproxil fumarate: In combination studies evaluating the in vitro antiviral activity of EFV and FTC together, EFV and tenofovir together and FTC and tenofovir together, additive to synergistic antiviral effects were observed.

Efavirenz: The concentration of EFV inhibiting replication of wild-type laboratory adapted strains and clinical isolates in cell culture by 90–95% ($EC_{90–95}$) ranged from 1.7–25 nM in lymphoblastoid cell lines, peripheral blood mononuclear cells, and macrophage/monocyte cultures. 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.

Emtricitabine: The in vitro antiviral activity of FTC against laboratory and clinical isolates of HIV was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. The EC_{50} (50% effective concentration) values for FTC were in the range of 0.0013–0.64 μM (0.0003–0.158 μg/mL). Emtricitabine displayed antiviral activity in vitro against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 0.007–0.075 μM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 0.007–1.5 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 0.04–8.5 μM. Tenofovir displayed antiviral activity in vitro against HIV-1 clades A, B, C, D, E, F, G, and O (EC_{50} values ranged from 0.5–2.2 μM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 1.6 μM to 4.9 μM).

Cardiac Electrophysiology:
Efavirenz: The effect of EFV on the QTc interval was evaluated in an open-label, positive and placebo-controlled, fixed single sequence 3-period, 3-treatment crossover QT study in 58 healthy subjects enriched for CYP2B6 polymorphisms. The mean Cmax of EFV in subjects with CYP2B6 *6/*6 genotype following the administration of 600 mg daily dose for 14 days was 2.25-fold the mean Cmax observed in subjects with CYP2B6 *1/*1 genotype. A positive relationship between EFV concentration and QTc prolongation was observed. Based on the concentration-QTc relationship, the mean QTc prolongation and its upper bound 90% confidence interval are 8.7 msec and 11.3 msec, respectively, in subjects with CYP2B6 *6/*6 genotype following the administration of 600 mg daily dose for 14 days (see **WARNINGS AND PRECAUTIONS**).

Pharmacokinetics

ATRIPLA:
One ATRIPLA Tablet was bioequivalent to one Sustiva Tablet (600 mg) plus one EMTRIVA Capsule (200 mg) plus one VIREAD Tablet (300 mg) following single-dose administration to fasting healthy subjects (N=45).

Efavirenz:
In HIV-infected patients time-to-peak plasma concentrations were approximately 3–5 hours and steady-state plasma concentrations were reached in 6–10 days. In 35 patients receiving EFV 600 mg once daily, steady-state C_{max} was 12.9 μM, C_{min} was 5.6 μM, and AUC was 184 μM/h. Efavirenz is highly bound (approximately 99.5–99.75%) to human plasma proteins, predominantly albumin. Following administration of ^{14}C-labeled EFV, 14–34% of the dose was recovered in the urine (mostly as metabolites) and 16–61% was recovered in feces (mostly as parent drug).

In vitro studies suggest CYP3A4 and CYP2B6 are the major isozymes responsible for EFV metabolism. Efavirenz has been shown to induce P450 enzymes, resulting in induction of its own metabolism.

Efavirenz has been shown in vivo to cause hepatic enzyme induction, thus increasing the biotransformation of some drugs metabolized by CYP3A4 and CYP2B6. In vitro studies have demonstrated that EFV inhibits 2C9, 2C19 and 3A4 isozymes with K_i values (8.5–17 μM) in the range of observed EFV plasma concentrations. In in vitro studies, EFV did not inhibit CYP2E1 and inhibited CYP2D6 and CYP1A2 (K_i values 82–160 μM) only at concentrations well above those achieved clinically. Coadministration of EFV with drugs primarily metabolized by 2C9, 2C19, and 3A4 isozymes may result in altered plasma concentrations of the coadministered drug. Drugs which induce CYP3A4 activity would be expected to increase the clearance of EFV resulting in lowered plasma concentrations.

Efavirenz plasma exposure may be increased in patients with the homozygous G516T genetic variant of the CYP2B6 isozyme. The clinical implications of such an association are unknown; however, the potential for an increased frequency and severity of EFV-associated adverse events cannot be excluded.

Efavirenz has a terminal half-life of 52–76 hours after single doses and 40–55 hours after multiple doses.

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

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

Effect of Food on Oral Absorption

ATRIPLA has not been evaluated in the presence of food. Administration of EFV tablets with a high fat meal increased the mean AUC and C_{max} of EFV by 28% and 79%, respectively, compared to administration in the fasted state. Compared to fasted

administration, dosing of TDF/FTC 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 FTC exposures.

Special Populations and Conditions

Pediatrics and Geriatrics: Pharmacokinetics of tenofovir have not been evaluated in children (<18 years). Efavirenz has not been studied in children below 3 years of age or who weigh less than 13 kg. Emtricitabine has been studied in pediatric patients from 3 months to 17 years of age. ATRIPLA is not recommended for pediatric administration. Pharmacokinetics of EFV, FTC, and tenofovir have not been fully evaluated in the elderly (>65 years of age).

Race:
Efavirenz: The pharmacokinetics of EFV in patients appear to be similar among the ethnic groups studied.

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

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 administration of TDF.

Gender: Efavirenz, FTC and tenofovir pharmacokinetics are similar in male and female patients.

Hepatic Insufficiency: In a multiple-dose EFV pharmacokinetics study (600 mg daily), the mean C_{max} and mean AUC of EFV in patients with mild hepatic impairment (Child-Pugh Class A, n=6) were 20.3 ± 15.5 μM (mean±SD) and 351 ± 336.9 μM•h (mean±SD), respectively, compared with those in controls (n=6; C_{max}= 28.4 ± 27.35 μM, AUC = 506 ±581 μM•h). There were insufficient data to determine whether moderate or severe hepatic impairment (Child-Pugh Class B or C) affects EFV pharmacokinetics. The pharmacokinetics of tenofovir following a 300 mg single dose of TDF have been studied in non-HIV infected subjects with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in subjects with hepatic impairment compared with unimpaired subjects. The pharmacokinetics of FTC has not been studied in patients with hepatic impairment; however, FTC has not been shown to be significantly metabolized by liver enzymes, so the impact of liver impairment should be limited **(**see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic)**.

Renal Insufficiency: The pharmacokinetics of EFV have not been studied in patients with renal insufficiency; however, less than 1% of EFV is excreted unchanged in the urine, so the impact of renal impairment on EFV elimination should be minimal. The pharmacokinetics of FTC and tenofovir are altered in patients with renal insufficiency **(**see **WARNINGS AND PRECAUTIONS, Renal, Nephrotoxicity)**. In patients with creatinine clearance

<50 mL/min, C_{max} and $AUC_{0-\infty}$ of FTC and tenofovir were increased. Because ATRIPLA is a fixed dose combination, it should not be prescribed for patients requiring dosage adjustment such as those with moderate to severe renal impairment (creatinine clearance <50 mL/min).

STORAGE AND STABILITY

Store at 15–30° C (59–86° F).

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

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ATRIPLA is available as tablets. Each tablet contains 600 mg of EFV, 200 mg of FTC and 300 mg of TDF (which is equivalent to 245 mg of tenofovir disoproxil), as active ingredients. The tablets also include the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The tablets are coated with Opadry II Pink 85F94172 which contains iron oxide black, iron oxide red, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide. The tablets are pink, capsule-shaped and film-coated, debossed with "123" on one side and plain-faced on the other side. Each bottle contains 30 tablets and a silica gel desiccant and is closed with a child-resistant closure.

PART II. SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

ATRIPLA Tablets are fixed dose combination tablets containing EFV, FTC and TDF. Sustiva is the brand name for EFV, a non-nucleoside reverse transcriptase inhibitor. EMTRIVA is the brand name for FTC, a synthetic nucleoside analog of cytidine. VIREAD is the brand name for tenofovir disoproxil fumarate (also known as TDF), which is converted in vivo to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate. All three compounds exhibit inhibitory activity against HIV-1 reverse transcriptase. VIREAD and EMTRIVA are the components of TRUVADA.

ATRIPLA Tablets are for oral administration. Each tablet contains 600 mg of EFV, 200 mg of FTC and 300 mg of TDF (which is equivalent to 245 mg of tenofovir disoproxil), as active ingredients. The tablets also include the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The tablets are coated with Opadry II Pink 85F94172 which contains iron oxide black, iron oxide red, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Efavirenz:

Drug Substance

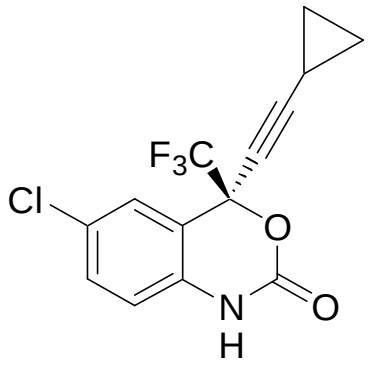
Common Name: efavirenz (USAN)

Chemical Name: (S)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2*H*-3,1-benzoxazin-2-one.

Empirical Formula: $C_{14}H_9ClF_3NO_2$

Molecular Weight: 315.68

Structural Formula:



Physicochemical Properties:

Description: Efavirenz is a white to slightly pink crystalline powder.

Solubility: It is practically insoluble in water (<10 μg/mL). The pKa is 10.2. The partition coefficient (log P) is = 5.4.

Emtricitabine:

Drug Substance

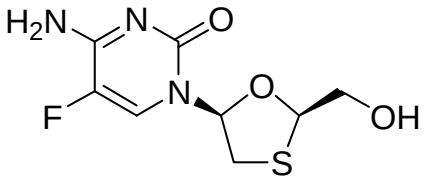
Common Name: emtricitabine (USAN)

Chemical Name: 5-fluoro-1-(2*R*,5*S*)-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine

Empirical Formula: $C_8H_{10}FN_3O_3S$

Molecular Weight: 247.24

Structural Formula:



Physicochemical Properties:

Description: Emtricitabine is a white to off-white crystalline powder.

Solubility: The solubility is approximately 112 mg/mL in water at 25 °C. The partition coefficient (log P) is –0.43 and the pKa is 2.65.

Tenofovir disoproxil fumarate:

Drug Substance

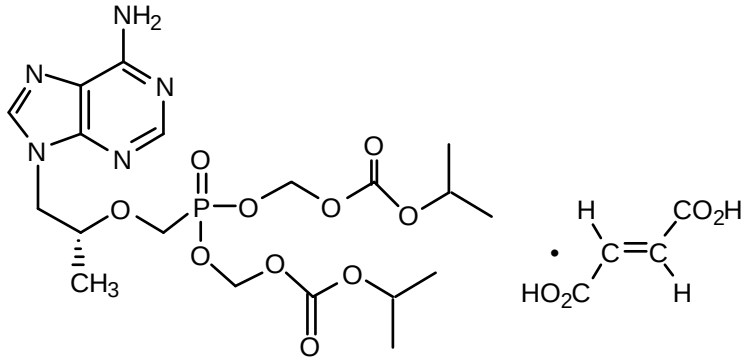
Common Name: tenofovir disoproxil fumarate (USAN)

Chemical Name: 9-[(*R*)-2-[[bis[[(isopropoxycarbonyl)oxy]methoxy]phosphinyl]-methoxy]propyl]adenine fumarate (1:1)

Empirical Formula: $C_{19}H_{30}N_5O_{10}P \bullet C_4H_4O_4$

Molecular Weight: 635.52

Structural Formula:



Physicochemical Properties:

Description: Tenofovir disoproxil fumarate is a white to off-white crystalline powder.

Solubility: The solubility is 13.4 mg/mL in water at 25 °C. The partition coefficient (log P) is 1.25 and the pKa is 3.75.

CLINICAL TRIALS

Study Demographics and Trial Design

Description of Clinical Studies

For safety and efficacy studies using Sustiva, EMTRIVA or VIREAD in combination with other antiretroviral agents, also consult the Product Monographs for these products.

Study 934

Study 934 was a phase III 144-week open-label randomized non-inferiority clinical study comparing the safety and efficacy of a once-daily regimen containing the individual agents EFV, FTC and TDF versus the fixed-dose combination of lamivudine and zidovudine (Combivir®) administered twice-daily and EFV once daily in HIV-1 infected antiretroviral treatment-naive patients. Patients in both arms of Study 934 who completed 144 weeks were given the option to roll-over into an open-label extension phase of the study and switch their ARV regimen to the once-daily fixed-dose combination single tablet regimen, EFV/FTC/TDF (ATRIPLA) for an additional 96 weeks.

In this study, 59% of patients 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); 41% had CD4+ cell counts <200 cells/mm^3 and 51% of patients had baseline viral loads >100,000 copies/mL.

Table 13. Study 934 EFV+FTC+TDF Compared with EFV+Lamivudine/Zidovudine

Study Number	Trial Design	Dosage, Route of Administration and Duration	Study Subjects	Mean Age	Gender
GS-01-934	Randomized, open-label, parallel, multicenter, active controlled study. **Arm 1:** FTC+TDF+ EFV **Arm 2:** lamivudine/ zidovudine+ EFV	**Arm 1[1]:** EFV 600 mg once daily, FTC 200 mg once and TDF 300 mg once daily; Oral administration. **Arm 2:** EFV 600 mg once daily and Combivir (lamivudine/ zidovudine) 150/300 mg twice daily. Oral administration. 144 weeks	Antiretroviral naive patients (HIV-1 RNA >10,000 copies/mL) (N=517 randomized)	Mean 38 years (18–80)	Male: 86% Female: 14%

[1]From weeks 96 to 144 of the study, patients randomized to FTC+TDF received FTC /TDF fixed-dose combination (Truvada) with EFV in place of FTC+TDF with EFV.

Study 073

Study 073 was a 48-week open-label, randomized clinical study in patients with stable virologic suppression on combination antiretroviral therapy. The study compared the efficacy of ATRIPLA to antiretroviral therapy consisting of at least two nucleoside reverse transcriptase inhibitors (NRTIs) administered in combination with a protease inhibitor (with or without ritonavir) or a non-nucleoside reverse transcriptase inhibitor. At baseline, patients had been virologically suppressed (HIV-1 RNA <200 copies/mL) on their current antiretroviral therapy for at least 12 weeks prior to study entry, and had no known HIV-1 substitutions conferring resistance to the components of ATRIPLA or history of virologic failure. At baseline, 140 subjects (47%) were receiving an NNRTI-based regimen and 160 subjects (53%) were receiving a PI-based regimen.

Table 14. Study 073 ATRIPLA Compared with 2 NRTI+NNRTI or 2 NRTI+PI (+/- Ritonavir)

Study Number	Trial Design	Dosage, Route of Administration and Duration	Study Subjects	Mean Age	Gender
AI266073	Open-label, randomized, parallel multicenter, active-controlled study.	**Arm 1:** ATRIPLA once daily. Oral administration. 48 weeks **Arm 2:** Standard Baseline Regimen (SBR)* either 2 NRTI +NNRTI or PI (+/- ritonavir). Oral administration. 48 weeks	Virologically suppressed (≥ 3 months) HIV-1 infected patients (HIV-1 RNA <200 copies/mL) (N=306 randomized)	Mean 43 years (22–73)	Male : 88% Female: 12%

*Dosage and dosing frequency administered according to manufacturers' dosing instructions.

Patients were randomized in a 2:1 ratio to switch to ATRIPLA (N=203) or stay on their baseline regimen (SBR) (N=97). Patients had a mean age of 43 years (range 22 to 73 years), 88% were male, 68% were white, 29% were black or African-American, and 3% were of other races. At baseline, median CD4+ cell count was 516 cells/mm^3 and all but 11 patients (3.7%) had HIV-1 RNA <50 copies/mL. The median time since onset of antiretroviral therapy was 3 years.

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 **VIROLOGY, Resistance and Cross Resistance)**.

Study Result

Efavirenz, FTC, and TDF

Study 934: EFV+FTC+TDF Compared with EFV+Lamivudine/Zidovudine

Treatment outcomes through 48 and 144 weeks for those patients who did not have EFV resistance at baseline are presented in Table 15.

Table 15. Outcomes of Randomized Treatment at Weeks 48 and 144 (Study 934)

Outcomes	At Week 48		At Week 144[1]	
	FTC+TDF+EFV (N=244)	3TC/AZT+EFV (N=243)	FTC+TDF+EFV (N=227)	3TC/AZT+EFV (N=229)
Responder[2]	84%	73%	71%	58%
Virologic Failure[3]	2%	4%	3%	6%
Rebound	1%	3%	2%	5%
Never Suppressed	0%	0%	0%	0%
Change in Antiretroviral Regimen	1%	1%	1%	1%
Death	<1%	1%	1%	1%
Discontinued Due to Adverse Event	4%	9%	5%	12%
Discontinued for Other Reasons[4]	10%	14%	20%	22%

1. Patients who did not consent to continue study beyond Week 48 were excluded from analysis.
2. Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Week 48 and 144.
3. Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Week 48 and 144.
4. Includes lost to follow-up, patient withdrawal, non-compliance, protocol violation and other reasons.

In this study, EFV+FTC+TDF demonstrated statistically significant superiority to lamivudine/zidovudine in combination with EFV in achieving and maintaining HIV-1 RNA <400 copies/mL through 48 and 144 weeks (Table 15). The difference in the percentages of responders, stratified by baseline CD4 cell count (< or ≥200 cells/mm^3), between the EFV+FTC+TDF group and the EFV+lamivudine/zidovudine group was 11.4%, and the 95% CI was 4.3% to 18.6% (p=0.002) at Week 48 and was 13% at Week 144, 95% CI= 4% to 22% (p=0.004). Through 48 weeks of therapy, 80% and 70% of patients in the EFV+FTC+TDF and the EFV+lamivudine/zidovudine arms, respectively, achieved and maintained HIV-1 RNA <50 copies/mL (64 and 56%, respectively, through Week 144). The difference in the percentages of responders stratified by baseline CD4 cell count (< or ≥200 cells/mm^3) between the EFV+FTC+TDF group and the EFV+lamivudine/zidovudine group was 9.1%, and the 95% CI was 1.6% to 16.6% (p=0.02) at Week 48 and was 8% at Week 144, 95% CI = -1% to 17% (p=0.082). The mean increase from baseline in CD4 cell count was 190 cells/mm^3 for the EFV+FTC+TDF arm, and 158 cells/mm^3 for the EFV+lamivudine/zidovudine arm (p=0.002) at Week 48 (312 and 271 cells/mm^3, respectively, at Week 144, p=0.089).

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.

Study 073: ATRIPLA Compared with 2 NRTI+NNRTI or 2 NRTI+PI (+/- Ritonavir)

Table 16 summarizes treatment outcomes through week 48.

Table 16. Outcomes of Randomized Treatment at Week 48 (Study 073)

Outcomes	ATRIPLA (N=203)	Stayed on Baseline Regimen (SBR) (N=97)
Responder[a]	89% (87%)	88% (85%)
Virologic failure[b]	1% (2%)	1% (4%)
Death	0%	0%
Discontinued due to adverse event	5%	1%
Discontinued for other reasons[c]	5%	10%

a. Patients who maintained confirmed HIV-1 RNA <200 copies/mL (<50 copies/mL) through Week 48. Primary endpoint of the study was HIV-1 RNA <200 copies/mL
b. Virologic failure defined as rebound [two consecutive HIV-1 RNA ≥200 copies/mL (≥50 copies/mL) or last observed HIV RNA ≥200 copies/mL (≥50 copies/mL)].
c. Includes lost to follow-up, patient consent withdrawal, investigator's discretion, and protocol violation.

The responder difference (HIV-1 RNA <200 copies/mL), ATRIPLA minus SBR, was 1% (95% CI: −7%, 9%, p=0.82) at week 48. ATRIPLA was non-inferior to SBR in this study. At week 48, the median change from baseline in CD4+ cell count was 3 cells/mm^3 in the ATRIPLA group and 9 cells/mm^3 in the SBR group.

When treatment responses were evaluated at 48 weeks by baseline treatment regimen strata (NNRTI or PI), 92% vs. 84% of patients on prior NNRTI-based antiretroviral therapy maintained HIV-1 RNA <200 copies/mL when randomized to switch to ATRIPLA vs. continue SBR, respectively. For patients on prior PI-based antiretroviral therapy, 87% vs. 90% of patients maintained HIV-1 RNA <200 copies/mL when randomized to receive ATRIPLA vs. SBR, respectively.

Comparative Bioavailability Studies

Study GS-US-177-0105 was a single-dose, randomized, open-label, two-way crossover study conducted in 45 healthy male and female adults to establish comparative bioavailability between the combination tablet (containing 600 mg EFV/200 mg FTC/300 mg TDF) and concurrent administration of the individual dosage forms, the Sustiva (EFV) 600 mg tablet, the EMTRIVA (FTC) 200 mg capsule and the VIREAD (TDF) 300 mg tablet, administered under fasting conditions, by evaluation of C_{max} and AUC of EFV, FTC and tenofovir. The bioavailability of one tablet of the fixed dose combination containing 600 mg EFV/200 mg FTC/300 mg TDF was found to be comparable to the bioavailability of one dose of the three individual dosage forms taken in combination. The results of Study GS-US-177-0105 are summarized in Tables 17, 18 and 19 below.

Table 17. Summary of EFV Pharmacokinetic Parameters (GS-US-177-0105) – Fasted

EFV 600mg From Measured Data
Geometric Mean
Arithmetic Mean (CV%)

Parameter	Test Treatment B[2]	Reference Treatment A[1]	% Ratio of Geometric Means[5]	90% Confidence Interval[5]
AUC_{0-72} (ng•h/mL)	52098.79 53366.2 (22.2)	54570.04 56352.5 (22.9)	95.47	(90.69, 100.51)
AUC_I (ng•h/mL)	139109.1 146074.9 (33.1)	145097.8 155518.6 (34.6)	95.87	(89.63, 102.55)
C_{max} (ng/mL)	2179.16 2264.3 (26.8)	2205.86 2308.6 (30.3)	98.79	(92.28, 105.76)
T_{max}[3] (h)	3.50 (2.00–8.00)	3.50 (1.50–5.50)		
$T_{½}$[4] (h)	180.6 (45.3)	182.5 (38.3)		

1. Treatment A = concurrent administration of Sustiva (EFV) 600 mg tablet , EMTRIVA (FTC) 200 mg capsule and VIREAD (TDF) 300 mg tablet to fasted subjects.
2. Treatment B = 600 mg EFV/200 mg FTC/300 mg TDF combination tablet administered to fasted subjects.
3. Expressed as the median (range) only.
4. Expressed as the arithmetic mean (CV%) only.
5. Based on geometric least squares mean.

Table 18. Summary of FTC Pharmacokinetic Parameters (GS-US-177-0105) – Fasted

FTC 200mg From Measured Data
Geometric Mean
Arithmetic Mean (CV%)

Parameter	Test Treatment B[2]	Reference Treatment A[1]	% Ratio of Geometric Means[5]	90% Confidence Interval[5]
AUC_T (ng•h/mL)	10523.83 10682.6 (18.1)	10740.78 10874.4 (14.9)	97.98	94.90–101.16
AUC_I (ng•h/mL)	10694.43 10854.9 (17.9)	10916.98 11054.3 (14.9)	97.96	94.86–101.16
C_{max} (ng/mL)	2066.48 2130.6 (25.3)	2325.96 2384.4 (20.4)	88.84	84.02–93.94
T_{max}[3] (h)	1.50 (1.00–5.00)	1.50 (0.77–2.50)		
$T_{½}$[4] (h)	14.5 (53.8)	14.6 (47.8)		

1. Treatment A=concurrent administration of Sustiva (EFV) 600 mg tablet , EMTRIVA (FTC) 200 mg capsule and VIREAD (TDF) 300 mg tablet to fasted subjects.
2. Treatment B = 600 mg EFV/200 mg FTC/300 mg TDF combination tablet administered to fasted subjects.
3. Expressed as the median (range) only.
4. Expressed as the arithmetic mean (CV%) only.
5. Based on geometric least squares mean.

Table 19. Summary of Tenofovir Pharmacokinetic Parameters (GS-US-177-0105) – Fasted

Tenofovir 300mg From Measured Data Geometric Mean Arithmetic Mean (CV%)				
Parameter	**Test Treatment B[2]**	**Reference Treatment A[1]**	**% Ratio of Geometric Means[5]**	**90% Confidence Interval[5]**
AUC_T (ng•h/mL)	1845.03 1948.8 (32.9)	1858.15 1969.0 (32.8)	99.29	91.02–108.32
AUC_I (ng•h/mL)	2218.24 2314.0 (29.2)	2208.41 2319.4 (30.3)	100.45	93.22–108.23
C_{max} (ng/mL)	307.25 325.1 (34.2)	335.93 352.9 (29.6)	91.46	84.64–98.83
T_{max}[3] (h)	1.00 (0.50–3.50)	0.75 (0.50–2.00)		
$T_{½}$[4] (h)	18.9 (20.8)	17.8 (22.6)		

1. Treatment A=concurrent administration of Sustiva (EFV) 600 mg tablet , EMTRIVA (FTC) 200 mg capsule and VIREAD (TDF) 300 mg tablet to fasted subjects
2. Treatment B=600 mg EFV/200 mg FTC/300 mg TDF combination tablet administered to fasted subjects.
3. Expressed as the median (range) only.
4. Expressed as the arithmetic mean (CV%) only.
5. Based on geometric least squares mean.

DETAILED PHARMACOLOGY

VIROLOGY (MICROBIOLOGY)

Efavirenz:

Efavirenz is a non-nucleoside reverse transcriptase (RT) inhibitor of human immunodeficiency virus type 1 (HIV-1). Efavirenz is predominantly a non-competitive inhibitor of HIV-1 RT. HIV-2 RT and human cellular DNA polymerases α, β, γ, and δ are not inhibited by EFV.

Emtricitabine:

Emtricitabine, a synthetic nucleoside analog of cytidine, is phosphorylated by cellular enzymes to form FTC 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 polymerases α, β, ε, and mitochondrial DNA polymerase γ.

Tenofovir disoproxil fumarate:
Tenofovir disoproxil fumarate is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir disoproxil fumarate 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 in vitro antiviral activity of FTC and EFV together, EFV and tenofovir together and FTC and tenofovir together, additive to synergistic antiviral effects were observed.

Efavirenz:
The clinical significance of in vitro susceptibility of HIV-1 to EFV has not been established. The in vitro antiviral activity of EFV was assessed in lymphoblastoid cell lines, peripheral blood mononuclear cells (PBMCs) and macrophage/monocyte cultures enriched from PBMCs. The concentration of EFV inhibiting replication of wild-type laboratory adapted strains and clinical isolates in cell culture by 90–95% ($EC_{90–95}$) ranged from 1.7 to ≤25nM. Efavirenz demonstrated additive to synergistic 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 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.

Emtricitabine:
The in vitro antiviral activity of FTC against laboratory and clinical isolates of HIV was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. The EC_{50} values for FTC were in the range of 0.0013–0.64 μM (0.0003–0.158 μg/mL). In drug combination studies of FTC with nucleoside reverse transcriptase inhibitors (abacavir, lamivudine, stavudine, zalcitabine, and zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, EFV, and nevirapine), and protease inhibitors (amprenavir, nelfinavir, ritonavir, and saquinavir), additive to synergistic effects were observed. Most of these drug combinations have not been studied in humans. Emtricitabine displayed antiviral activity in vitro against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 0.007–0.075 μM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 0.007–1.5 μM).

Tenofovir disoproxil fumarate:
The in vitro antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The EC_{50} values for tenofovir were in the range of 0.04–8.5 μM. In drug combination studies of tenofovir with nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, zalcitabine, and zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, EFV, and nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, and saquinavir), additive to synergistic effects were observed. Most of these drug combinations have not been studied in humans. Tenofovir displayed antiviral activity in vitro against HIV-1 clades A, B, C, D, E, F, G, and O (IC_{50} values ranged from 0.5–2.2 μM).

Resistance

Efavirenz, emtricitabine and tenofovir disoproxil fumarate:
HIV-1 isolates with reduced susceptibility to the combination of FTC 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 addition, a K70E substitution in HIV-1 reverse transcriptase has been selected by tenofovir and results in low-level reduced susceptibility to abacavir, FTC, tenofovir, and lamivudine.

In a clinical study of treatment-naïve patients (Study 934, see **Clinical Studies**) resistance analysis was performed on HIV isolates from all virologic failure patients with >400 copies/mL of HIV-1 RNA at Week 144 or early discontinuations. The resistance analysis population consisted of 19/244 (8%) patients in the FTC+TDF group and 29/243 (12%) patients in the zidovudine/lamivudine fixed-dose combination group with available genotypic data. Genotypic resistance to EFV, predominantly the K103N mutation, was the most common form of resistance that developed. Resistance to EFV occurred in 13/19 (68%) analyzed patients (13/244, 5% of total patients) in the FTC+TDF group and in 21/29 (72%) analyzed patients (21/243, 9% of total patients) in the zidovudine/lamivudine fixed-dose combination group. The M184V amino acid substitution, associated with resistance to FTC and lamivudine, was observed in 2/19 (11%) analyzed patient isolates (2/244, 0.8% of total patients) in the FTC+TDF group and in 10/29 (34%) analyzed patient isolates (10/243, 4.1% of total patients) in the zidovudine/lamivudine group; this difference was statistically significant (p=0.021). Through 144 weeks of Study 934, no patients developed a detectable K65R mutation in their HIV as analyzed through standard genotypic analysis.

Only limited resistance data are available from a clinical study of treatment-experienced patients with stable virologic suppression and no history of virologic failure (Study 073, see **CLINICAL TRIALS** section) since virologic failure was observed in only 3 subjects in the ATRIPLA treatment group. One of the 3 subjects who experienced virologic failure on ATRIPLA had confirmed development of resistance, specifically the K103N EFV resistance mutation only.

In a clinical study of treatment-naïve patients, isolates from 8/47 (17%) analyzed patients receiving TDF developed the K65R substitution through 144 weeks of therapy; 7 of these

occurred in the first 48 weeks of treatment and one at Week 96. In treatment experienced patients, 14/304 (5%) of TDF 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:
HIV-1 isolates with reduced susceptibility to EFV (>380-fold increase in EC_{90}) compared to baseline emerged rapidly under selection in cell culture in the presence of drug.

Genotypic characterization 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. 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%).

Phenotypic (N=26) changes in evaluable HIV-1 isolates and genotypic (N=104) changes in plasma virus from selected patients treated with EFV in combination with indinavir, or with zidovudine plus lamivudine, were monitored. Clinical isolates with reduced susceptibility in vitro to EFV have been obtained. One or more RT mutations at amino acid positions 98, 100, 101, 103, 106, 108, 188, 190 and 225, and 227 were observed in all 102 of 104 patients with a frequency of at least 9% compared to baseline. The mutation at RT amino acid position 103 (lysine to asparagine) was the most frequently observed (≥90%). A mean loss in susceptibility (EC_{90}) to EFV of 47-fold was observed in 26 clinical isolates. Five clinical isolates were evaluated for both genotypic and phenotypic changes from baseline. Decreases in EFV susceptibility (range from 9 to >312-fold increase in EC_{90}) were observed for these isolates in vitro compared to baseline. All 5 isolates possessed at least one of the EFV-associated RT mutations. The clinical relevance of phenotypic and genotypic changes associated with EFV therapy has not been established.

Emtricitabine:
Emtricitabine-resistant isolates of HIV have been selected in vitro. Genotypic analysis of these isolates showed that the reduced susceptibility to FTC 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 vitro. These viruses expressed a K65R mutation in RT and showed a 2–4 fold reduction in susceptibility to tenofovir.

Cross-resistance

Efavirenz, emtricitabine and tenofovir disoproxil fumarate:
Cross-resistance has been recognized among NNRTIs. Cross-resistance has also been recognized among certain NRTIs. The M184V/I and/or K65R substitutions selected in vitro

by the combination of FTC and tenofovir are also observed in some HIV-1 isolates from subjects failing treatment with tenofovir in combination with either lamivudine or FTC, and either abacavir or didanosine. Therefore, cross-resistance among these drugs may occur in patients whose virus harbors either or both of these amino acid substitutions. Delaviradine 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 EFV in cell culture.

Efavirenz:
Rapid emergence of HIV-1 strains that are cross-resistant to non-nucleoside RT inhibitors has been observed in vitro. Thirteen clinical isolates previously characterized as EFV-resistant were also phenotypically resistant to nevirapine and delavirdine in vitro compared to baseline. Clinically derived zidovudine-resistant HIV-1 isolates tested in vitro retained susceptibility to EFV. Cross-resistance between EFV and HIV protease inhibitors is unlikely because of the different enzyme targets involved.

Emtricitabine:
Emtricitabine-resistant isolates (M184V/I) were cross-resistant to lamivudine and zalcitabine but retained susceptibility in vitro to didanosine, stavudine, tenofovir, zidovudine, and NNRTIs (delavirdine, EFV, and nevirapine). Isolates from heavily treatment-experienced patients containing the M184V/I amino acid substitution in the context of other NRTI resistance-associated substitutions may retain susceptibility to tenofovir. HIV-1 isolates containing the K65R substitution, selected in vivo by abacavir, didanosine, tenofovir, and zalcitabine, demonstrated reduced susceptibility to inhibition by FTC. Viruses harboring mutations conferring reduced susceptibility to stavudine and zidovudine (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) or didanosine (L74V) remained sensitive to FTC. HIV-1 containing the K103N substitution associated with resistance to NNRTIs was susceptible to FTC.

Tenofovir disoproxil fumarate:
Cross-resistance has been observed among NRTIs. 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 FTC and lamivudine. Therefore, cross-resistance among these drugs may occur in patients whose virus harbors the K65R mutation. The K70E substitution selected by TDF results in reduced susceptibility to abacavir, didanosine, FTC, and lamivudine. 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. Multinucleoside resistant HIV-1 with a T69S double insertion mutation in the RT showed reduced susceptibility to tenofovir.

TOXICOLOGY

For additional information on toxicology, reproductive toxicology, mutagenicity and carcinogenicity, please consult the Product Monographs for Sustiva, EMTRIVA, and VIREAD.

Carcinogenesis

Efavirenz:
Oral carcinogenicity studies in mice and rats were carried out with EFV. 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 at all doses were increased above background in females. No increases in tumor incidence above background were seen in males. The systemic exposure (based on AUCs) in mice was approximately 1.7-fold that in humans receiving the 600-mg/day dose. In studies in which rats were administered EFV at doses of 0, 25, 50, or 100 mg/kg/day for 2 years, no increases in tumor incidence above background were observed. The exposure to EFV in rats at all doses was lower than that in humans.

The findings from the EFV mouse carcinogenicity study may not represent a significant risk to patients based upon the following: An increase in the incidence of hepatic tumors in EFV-treated mice was not unexpected as EFV is known to induce hepatic drug-metabolizing enzyme activity and enzyme inducers are known to increase the incidence of hepatic tumors in rodents, but not in humans. While the cause of the increased incidence of pulmonary tumors is not known, this finding also may not constitute a significant risk for patients given EFV because: (1) EFV is not genotoxic, (2) the strain of mice used in these studies is documented to have a high spontaneous background incidence of this tumor type, and (3) a decrease in the incidence of pulmonary tumors was observed in EFV-treated male mice. In male mice, plasma EFV concentrations were equal to or greater than in female mice.

Emtricitabine:
In long-term oral carcinogenicity studies of FTC, no drug-related increase in tumor incidence was 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/kg/day (31 times the human systemic exposure at the therapeutic dose).

Tenofovir disoproxil fumarate:
Long-term oral carcinogenicity studies were conducted in mice and rats receiving TDF. In the mouse study, one male and two female mice in the 600 mg/kg/day group (15 times the human systemic exposure at the recommended human dose of 300 mg/day) had duodenal tumors. The mechanism underlying this effect is uncertain but may relate to high local drug concentrations in the gastrointestinal tract. No treatment-related tumors were seen in mice in the 100 or 300 mg/kg/day groups. In the rat study at doses of 30, 100, and 300 mg/kg/day (approximately 5 times human exposure), no treatment-related increase in tumor incidence was observed.

Mutagenesis

Efavirenz:
Efavirenz was not genotoxic in a battery of in vitro and in vivo genotoxicity assays. This included assays in four in vitro assay systems: (1) bacterial mutation assays in *Salmonella typhimurium* and *Escherichia coli*, (2) a Chinese hamster ovary (CHO) cell/hypoxanthine-

guanine phosphoribosyl-transferase (HGPRT) forward mutation assay, (3) a chromosome aberration assay in human peripheral lymphocytes, and (4) a chromosome aberration assay in CHO cells, and in one in vivo system (mouse micronucleus assay). All assays were conducted employing maximally soluble or minimally toxic doses/concentrations of EFV.

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

Tenofovir disoproxil fumarate:
Tenofovir disoproxil fumarate was not mutagenic in the in vitro bacterial mutation (Ames) assay (*Salmonella-Eschericia coli*/Mammalian-Microsome Reverse Mutation Assay) but was mutagenic in the in vitro mouse lymphoma assay (L5178Y TK +/– Forward Mutation Assay), with and without metabolic activation. Tenofovir disoproxil fumarate was not clastogenic in the in vivo mouse micronucleus assay at plasma exposure levels of more than 10x the human exposure.

Reproductive Toxicology

Efavirenz:
Malformations were observed in 3 of 20 fetuses/infants from EFV-treated cynomolgus monkeys versus 0 of 20 concurrent control animals. The pregnant monkeys were given 60 mg/kg/day of EFV throughout pregnancy (post-coital days 20-150) and plasma drug concentrations were similar to those in humans given 600 mg/day. Anencephaly and unilateral anophthalmia were observed in one fetus, microophthalmia was observed in another fetus, and cleft palate was observed in a third fetus.

No malformations were observed in fetuses from EFV-treated rats; however an increase in fetal resorptions and a slight increase in pup mortality was observed at doses that produced peak plasma concentrations and AUC values in pregnant female rats similar to or lower than those achieved in humans at the recommended clinical dose. Efavirenz was not teratogenic or embryotoxic when given to pregnant rabbits.

A 5–8% decrease in mean rat pup weights versus control, and a slight increase in pup mortality was observed at ≥ 50 mg/kg BID when EFV was given to pregnant rats during gestation and through lactation until weaning. Peak plasma concentrations and AUC values in rats were similar to or lower than those in humans at the recommended clinical dose. No EFV-related effects were observed on the fertility, mating behavior, sexual maturation, learning, or behavior of the F1 generation derived from female rats given 100 mg/kg BID.

In a five-week oral infant rhesus toxicity study, infant monkeys given 30 mg/kg BID exhibited slight transitory decreases in body weight gain and food intake. Doses of 45 mg/kg BID produced adverse clinical signs including; vomiting, lethargy, dehydration, poor appetite, and/or weakness and slight decreases in body weight gain.

No EFV-related effects were observed on the fertility or reproductive performance of female rats given 100 mg/kg BID, or on the reproductive performance or sperm motility and morphology of male rats given 200 mg/kg BID.

Efavirenz produced no reproductive toxicities when given to pregnant rabbits at the dose that produced peak plasma concentrations similar to and AUC values approximately half of those achieved in humans given 600 mg once daily of EFV.

Fetal exposure to EFV was documented in pregnant rats, rabbits and cynomolgus monkeys. Maternal and fetal blood concentrations were equivalent in pregnant rabbits and cynomolgus monkeys and fetal blood concentrations were approximately 25% to 49% lower than the corresponding maternal concentrations in pregnant rats. Results of these studies indicated that EFV crossed the placenta of all species tested.

The excretion of EFV into rat milk was demonstrated. Efavirenz milk concentrations in rats were approximately 8-fold higher than corresponding maternal EFV plasma concentrations.

Emtricitabine:
The incidence of fetal variations and malformations was not increased in embryofetal toxicity studies performed with FTC in mice at exposures (AUC) approximately 60-fold higher and in rabbits at approximately 120-fold higher than human exposures at the recommended daily dose.

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:
Tenofovir disoproxil fumarate had no adverse effects on embryo-fetal development in rats at doses 450 mg/kg/day and in rabbits at doses up to 300 mg/kg/day (14 and 19 times the human dose based on body surface area comparisons).

Tenofovir disoproxil fumarate had no adverse effects on fertility or general reproductive performance in rats at doses up to 600 mg/kg/day. In a study of effects on peri- and postnatal development in rats, reduced pup body weights, survival and delay in sexual maturation was in rats at the maternally toxic doses of 450 and 600 mg/kg (approximately 14 and 19 times the human dose based on body surface area comparisons). There were no adverse effects on growth, development, behavior, or reproductive parameters at non-maternally toxic doses (150 mg/kg/day).

Studies in rats and rhesus monkeys have demonstrated that tenofovir is secreted in milk.

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PART III. CONSUMER INFORMATION

PrATRIPLA®
(efavirenz/emtricitabine/tenofovir disoproxil fumarate) tablets

This leaflet is Part III of a three part "Product Monograph" published when ATRIPLA was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about ATRIPLA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
ATRIPLA contains 3 medicines, Sustiva® (efavirenz), EMTRIVA® (emtricitabine) and VIREAD® (tenofovir disoproxil fumarate; tenofovir DF), combined in one pill. EMTRIVA and VIREAD are HIV (human immunodeficiency virus) nucleoside/nucleotide analog reverse transcriptase inhibitors (NRTIs) and Sustiva is an HIV non-nucleoside analog reverse transcriptase inhibitor (NNRTI). VIREAD and EMTRIVA are components of TRUVADA®. ATRIPLA can be used alone as a complete regimen or in combination with other medications to treat people with HIV infection. ATRIPLA is for adults age 18 and older. ATRIPLA has not been studied in children under age 18 or adults over age 65.

What it does:
ATRIPLA helps block HIV reverse transcriptase, a chemical in your body (enzyme) that is needed for HIV to multiply. ATRIPLA lowers the amount of HIV in the blood (viral load). Lowering the amount of HIV in the blood lowers the chance of infections that happen when your immune system is weak (opportunistic infections).

HIV infection destroys CD4+ (T) cells, which are important to the immune system. The immune system helps fight infection. After a large number of T cells are destroyed, acquired immune deficiency syndrome (AIDS) develops. ATRIPLA may also help to increase the number of T cells (CD4+ cells).

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

ATRIPLA has not been shown to reduce the risk of passing HIV to others through sexual contact or blood contamination. Continue to practice safe sex and do not use or share dirty needles.

When it should not be used:
Together with your doctor, you need to decide whether ATRIPLA is right for you.

Do not take ATRIPLA if:
- you are taking any medication that is listed in this pamphlet under **"Drugs that must not be taken with ATRIPLA" (see INTERACTIONS WITH THIS MEDICATION).**
- you have or are at known risk for any type of bone disease or bone-related problems and have not discussed this with your doctor.
- you are allergic to ATRIPLA or any of its ingredients. The medicinal ingredients are efavirenz, emtricitabine and tenofovir DF **(see: What the important nonmedicinal ingredients are).**

What the medicinal ingredients are:
efavirenz
emtricitabine
tenofovir disoproxil fumarate (tenofovir DF)

What the important nonmedicinal ingredients are:
croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, black iron oxide, polyethylene glycol, polyvinyl alcohol, red iron oxide, talc and titanium dioxide.

What dosage forms it comes in:
ATRIPLA is available as tablets. Each tablet contains 600 mg of efavirenz, 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate (which is equivalent to 245 mg of tenofovir disoproxil), as active ingredients. The tablets are pink, modified capsule-shaped, film-coated, debossed with "123" on one side and plain-faced on the other side. Each bottle contains 30 tablets and a silica gel desiccant and is closed with a child-resistant closure.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

The class of medicines to which emtricitabine and tenofovir DF, two of the components of ATRIPLA, belongs (NRTIs) can cause a condition called lactic acidosis, together with an enlarged liver. This rare but serious side effect has occasionally been fatal.

- The symptoms of lactic acidosis include: feeling very weak, tired or uncomfortable; unusual or unexpected stomach discomfort; feeling cold; feeling dizzy or lightheaded; suddenly developing an irregular heartbeat. Lactic acidosis occurs more often in women, particularly if they are very overweight. You should consult your doctor immediately if such symptoms occur while you are receiving ATRIPLA.
- Non-specific symptoms of liver problems may include nausea, vomiting, stomach pain and yellowing of the skin and eyes.

If you notice these symptoms of lactic acidosis or liver problems, stop taking ATRIPLA and consult a doctor immediately.

- **"Flare-ups" of hepatitis B virus infection,** in which the disease suddenly returns in a worse way than before, can occur if you stop taking ATRIPLA. Do not stop taking ATRIPLA without your doctor's advice. If you stop taking ATRIPLA, tell your doctor immediately about any new, unusual or worsening symptoms that you notice after stopping treatment. After you stop taking ATRIPLA, your doctor will still need to check your health and take blood tests to check your liver. ATRIPLA is not approved for the treatment of hepatitis B virus infection.
- The most serious possible side effect is harm to the kidneys, including damage to kidney cells, kidney tissue inflammation and kidney failure. Your doctor may monitor your kidney function before beginning and while receiving ATRIPLA. Some patients treated with tenofovir DF (a component of ATRIPLA) have had kidney problems. Your doctor may need to perform additional blood tests if you have had kidney problems in the past or need to take another drug that can cause kidney problems.
- Tenofovir DF, a component of ATRIPLA, caused harm to the bones of animals. If you notice bone pain, suffer a bone fracture, or other bone problem, consult your doctor. **If you have bone problems, you may wish to discuss calcium and/or vitamin D supplementation with your doctor. The effect of supplementation with calcium and/or vitamin D is unknown.**
- Patients who experience dizziness, trouble concentrating or drowsiness should avoid driving or operating machinery.
- **Women should not become pregnant while taking ATRIPLA and for 12 weeks after stopping it.** Serious birth defects have been seen in animals and women treated with efavirenz (a component of ATRIPLA) during pregnancy. It is not known whether efavirenz caused these defects. A reliable form of barrier contraception must always be used even if you or your partner are using other methods of contraception such as the pill or other hormonal therapy (e.g. implants, injections). ATRIPLA may remain in your blood for a time after therapy is stopped. Therefore, you should continue use of a reliable form of contraception for 12 weeks after stopping treatment with ATRIPLA. If you are pregnant or become pregnant while taking ATRIPLA, your doctor may register you in the Antiretroviral Pregnancy Registry. The Registry monitors fetal outcomes in pregnant women using antiretroviral medicines.
- A small number of patients taking efavirenz, one of the components of ATRIPLA, have had severe depression, strange thoughts, or angry behavior. Some patients have had thoughts of suicide and a few patients have actually committed suicide. These problems tend to occur more often in patients with a history of mental illness. You should contact your doctor immediately if you think you are having these symptoms, so your doctor can decide whether you should continue to take ATRIPLA.
- Consult your doctor if you have a rash, since some rashes may be serious.

BEFORE you use ATRIPLA (efavirenz/ emtricitabine/tenofovir DF) talk to your doctor or pharmacist:

If you have ever had a previous life threatening skin reaction (e.g. Stevens-Johnson syndrome).

If you are breast-feeding or plan to breast-feed: Do not breast-feed if you have HIV or are taking ATRIPLA. HIV can be passed to your baby in your breast milk. All components of ATRIPLA (efavirenz, emtricitabine and tenofovir DF) can be passed to your baby in your breast milk and may cause harm to your baby. Talk to your doctor about the best way to feed your baby.

If you have other medical conditions: Let your doctor know if you have other medical conditions, especially liver or kidney problems, pancreatitis (inflammation of the pancreas), seizures or mental illness, or have or are at risk for bone disease or bone-related problems.

If you have or have had a heart rhythm disorder such as:

- lengthening of QT interval
- irregular heartbeat
- a heart condition, Torsades de pointes

If you are taking other medicines: Some medicines can interact when taken together, including prescription and non-prescription medicines, herbal products and dietary supplements **(see INTERACTIONS WITH THIS MEDICATION).**

Other Special Warnings: Your blood sugar levels (glucose) or levels of fats (lipids) in your blood may increase with HIV treatment. Your doctor may order blood tests for you.

INTERACTIONS WITH THIS MEDICATION

No drug interaction studies have been done with ATRIPLA.

Drugs that must not be taken with ATRIPLA:

- **Propulsid™ (cisapride)*, Versed® (midazolam), Halcion® (triazolam), ergot medications (for example Wigraine® and Cafergot®), Hismanal (astemizole)*, Seldane® (terfenadine)*, Vascor® (bepridil)* or Orap® (pimozide).** Taking these medications with ATRIPLA could create the potential for serious or life-threatening side effects.
- Zepatier® (elbasvir/grazoprevir), since Zepatier® may lose its effect.
- Vfend® (voriconazole), since it may lose its effect or may increase the chance of having side effects from ATRIPLA.
- **Do not take ATRIPLA if you are taking St. John's wort (*Hypericum perforatum*), or products containing St. John's wort.** St. John's wort is an herbal product sold as a dietary supplement. Taking St. John's wort may decrease ATRIPLA levels and may lead to increased viral load and possible resistance to efavirenz or resistance to the class of non-nucleoside reverse transcriptase inhibitors (NNRTIs).

*Not marketed in Canada.

It is also important to tell your doctor if you are taking any of the following:

- ATRIPLA should not be used with 3TC®, Combivir®, COMPLERA®, DESCOVY®, EMTRIVA, GENVOYA®, Heptovir®, HEPSERA®, Kivexa®, ODEFSEY™, Triumeq®, Trizivir®, TRUVADA®, STRIBILD®, VEMLIDY™ or VIREAD. ATRIPLA also should not be used with Sustiva® unless your doctor decides a dose adjustment is needed (e.g. with rifampin).
- Do not take ATRIPLA if you are on other medications that may affect your kidneys and you have not discussed this with your doctor. ATRIPLA should not be used at the same time or shortly after cidofovir, ganciclovir, vancomycin or aminoglycosides as this may harm the kidneys.
- Reyataz® (atazanavir sulfate), Fortovase®* or Invirase® (saquinavir); **these medicines need to be replaced with another medicine when taken with ATRIPLA. If your doctor does prescribe Reyataz and ATRIPLA, you may need to be monitored more carefully for side effects.**
- Biaxin® (clarithromycin). Biaxin may interact with ATRIPLA to affect the electrical activity of your heart. **Biaxin needs to be replaced with another medicine when taken with ATRIPLA.**
- Celsentri® (maraviroc).
- Crixivan® (indinavir), methadone, Mycobutin® (rifabutin), Zoloft® (sertraline), Wellbutrin® SR, Wellbutrin® XL, or Zyban® (bupropion); **these medicines may need to have their dose changed when taken with ATRIPLA.**
- Videx® or Videx EC ® (didanosine); tenofovir DF (a component of ATRIPLA) may increase the amount of didanosine in your blood, which could result in more side effects. **You may need to be monitored more carefully** if you are taking ATRIPLA and didanosine together. Also, the dose of didanosine may need to be changed.
- Kaletra® (lopinavir/ritonavir) or HARVONI® (ledipasvir/sofosbuvir) may increase the amount of tenofovir DF (a component of ATRIPLA) in your blood, which could result in more side effects. **You may need to be monitored more carefully** if you are taking ATRIPLA and Kaletra together or ATRIPLA and HARVONI together. Also, the dose of Kaletra may need to be changed.
- EPCLUSA® (sofosbuvir/velpatasvir) or VOSEVI™ (sofosbuvir/velpatasvir/voxilprevir) should not be used with ATRIPLA as it is expected to decrease the amount of velpatasvir (a component of EPCLUSA and VOSEVI) and voxilaprevir (a component of VOSEVI) in your blood, which may reduce the effectiveness of EPCLUSA or VOSEVI.
- Medicines for seizures [for example, Dilantin® (phenytoin), Tegretol® (carbamazepine), or phenobarbital]; your doctor may want to switch you to another medicine or check drug levels in your blood from time to time.

- Sporanox® (itraconazole) and Posanol® (posaconazole) may need to be replaced by another medicine when taken with ATRIPLA.
- The cholesterol-lowering medicines Lipitor® (atorvastatin), Pravachol® (pravastatin sodium), and Zocor® (simvastatin).
- Rifadin® (rifampin) or the rifampin-containing medicines Rofact® and Rifater®.
- Calcium channel blockers such as Cardizem® or Tiazac® (diltiazem), Covera HS®, Isoptin® SR or Tarka® (verapamil), and others.
- Immunosuppressants such as Neoral® (cyclosporine), Advagraf® or Prograf® (tacrolimus), Rapamune® or Torisel® (sirolimus).
- Hepatitis C antiviral agents such as Galexos® (simeprevir).
- Antimalarials such as Coartem®* and Riamet®* (artemether/lumefantrine). These medicines may interact with ATRIPLA to affect your heart. Malarone® (atovaquone/proguanil) (an antimalarial).
- The effect of combining alcohol or recreational (street, illicit) drugs with efavirenz has not been studied. Because they may interact with each other, speak with your doctor before you combine ATRIPLA with these drugs.

*Not marketed in Canada.

These are not all the medicines that may cause problems if you take ATRIPLA. Be sure to tell your doctor about all the medicines you take.

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

PROPER USE OF THIS MEDICATION

Stay under a doctor's care when taking ATRIPLA. Do not change your treatment or stop treatment without first talking with your doctor.

Take ATRIPLA every day exactly as your doctor prescribed it. Follow the directions from your doctor, exactly as written on the label. Set up a dosing schedule and follow it carefully.

When your ATRIPLA supply starts to run low, get more from your doctor or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short time. The virus may develop resistance to ATRIPLA and become harder to treat.

Only take medicine that has been prescribed specifically for you. Do not give ATRIPLA to others or take medicine prescribed for someone else.

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

Usual Adult Dose:

- The usual dose of ATRIPLA is one tablet orally (by mouth) once a day.
- ATRIPLA should be taken on an empty stomach. Taking ATRIPLA at bedtime may make some side effects less bothersome.

Overdosage:

In case of drug overdose, contact your healthcare practitioner (e.g. doctor), hospital emergency department or regional poison control centre, even if there are no symptoms.

Missed Dose:
It is important that you do not miss any doses. If you miss a dose of ATRIPLA, take it as soon as you remember that day. **Do not** take more than 1 dose of ATRIPLA in a day. **Do not** take 2 doses at the same time. Call your doctor or pharmacist if you are not sure what to do.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects of Sustiva, EMTRIVA and VIREAD are:

- Nervous system symptoms such as dizziness, trouble sleeping, drowsiness, trouble concentrating, unusual dreams
- Headache
- Diarrhea
- Nausea
- Vomiting
- Rash
- Flatulence (intestinal gas)
- Tiredness
- Itching
- Allergic reaction (including swelling of the face, lips, tongue or throat)
- Abdominal pain

Other side effects may include pancreatitis (inflammation

of the pancreas) and shortness of breath.

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

A small number of patients taking efavirenz, one of the components of ATRIPLA, have had severe depression, strange thoughts, or angry behavior. Some patients have had thoughts of suicide and a few patients have actually committed suicide. These problems tend to occur more often in patients with a history of mental illness. Contact your doctor immediately if you think you are having these symptoms so your doctor can decide whether you should continue to take ATRIPLA.

Changes in body fat have been seen in some patients taking antiretroviral therapy. These changes may include increased amounts of fat in the upper back and neck ("buffalo hump"), breast, and around the trunk. Loss of fat from the legs, arms and face may also happen. The cause and long-term health effects of these conditions are not known at this time.

Some patients have experienced serious liver problems including liver failure, resulting in transplantation or death. Most of these serious side effects occurred in patients with a chronic liver disease such as a hepatitis infection, but there have also been a few reports in patients without any existing liver disease.

Changes in your immune system (Immune Reconstitution Inflammatory Syndrome) can happen when you start taking HIV medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time, or you could develop an autoimmune disease in which your immune system reacts against your own body [e.g. Grave's disease (which affects the thyroid gland), Guillain-Barre syndrome (which affects the nervous system) or polymyositis (which affects the muscles)] and it may develop at any time, sometimes months after the start of HIV therapy. Sometimes symptoms can be severe, so if you develop high temperature (fever), joint or muscle pain, redness, rash, swelling or fatigue, or any new symptoms, contact your doctor right away.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
		Only if severe	**In all cases**	**doctor or pharmacist**
Common	**Effect: Serious psychiatric events** **Symptoms:** • Severe depression • Thoughts of suicide • Strange thoughts • Angry behavior		 ✓ ✓ ✓ ✓	
Uncommon	**Effect: Serious psychiatric events** **Symptoms:** • Catatonia (cannot move or talk for some time)		 ✓	
Uncommon	**Effect: Severe skin rash** **Symptoms:** • Blisters or peeling of the skin • Blisters or peeling of the mouth, lips and throat • Fever and general ill feeling.			 ✓ ✓ ✓
Rare	**Effect: Lactic acidosis** **Symptoms:** • Feeling very weak or tired • Unusual muscle pain • Stomach pain with nausea and vomiting • Feeling cold, especially in arms and legs • Feeling dizzy or lightheaded • Irregular heartbeat		 ✓ ✓ ✓ ✓ ✓ ✓	
Rare	**Effect: Hepatotoxicity (severe liver problems) with hepatomegaly (liver enlargement) and steatosis (fat in the liver)** **Symptoms:** • Jaundice (skin or the white part of eyes turns yellow) • Urine turns dark • Bowel movements (stools) turn light in color • Loss of appetite for several days or longer • Feeling sick to your stomach (nausea) • Lower stomach pain		 ✓ ✓ ✓ ✓ ✓ ✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
	Symptoms / Effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very Rare	**Effect: Flare-ups of hepatitis B virus infection following drug discontinuation** **Symptoms:** • Jaundice (skin or the white part of eyes turns yellow)		✓	
	• Urine turns dark		✓	
	• Bowel movements (stools) turn light in color		✓	
	• Loss of appetite for several days or longer		✓	
	• Feeling sick to your stomach (nausea)		✓	
	• Lower stomach pain		✓	
Rare	**Effect: Kidney problems** **Symptoms:** • You may have increased or decreased urination as well as increased thirst		✓	
	• You may have swelling of your legs and feet		✓	
	• You may feel listless and tired		✓	

Lactic acidosis is a medical emergency and must be treated in the hospital. You may be more likely to get lactic acidosis or serious liver problems if you are very overweight (obese) or have been taking nucleoside analog medicines, like ATRIPLA, for a long time.

Muscle pain, muscle weakness, bone pain and softening of the bone (infrequently contributing to fractures) have also been reported due to tenofovir DF (a component of ATRIPLA).

There have been other side effects in patients taking Sustiva, EMTRIVA or VIREAD. This is **not** a complete list of side effects. If you have questions about side effects, ask your doctor, nurse, or pharmacist. You should report any new or continuing symptoms to your doctor right away. Your doctor may be able to help you manage these side effects.

HOW TO STORE IT

- Keep ATRIPLA and all other medications out of reach and sight of children.
- ATRIPLA should be stored at 15–30 °C (59–86 °F). It should remain stable until the expiration date printed on the label.
- Do not keep your medicine in places that are too hot or cold.
- Do not keep medicine that is out of date or that you no longer need. If you throw any medicines away, make sure that children will not find them.
- Keep ATRIPLA in its original container and keep the container tightly closed.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 1908C
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the Medeffect™ Canada Web site at www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.

NOTE: Should you require information related to the management of side effects, please contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals, can be found at: www.gilead.ca or by contacting the sponsor, Gilead Sciences Canada, Inc., at: 1-866-207-4267

This leaflet was prepared by Gilead Sciences, LLC.

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ATRIPLA®, COMPLERA®, DESCOVY®, EMTRIVA®, EPCLUSA®, GENVOYA®, HARVONI®, HEPSERA®, SOVALDI®, STRIBILD®, TRUVADA®, VIREAD®, and VOSEVI™ are trademarks of Gilead Sciences, Inc. or its related companies.

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