HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ATRIPLA safely and effectively. See full prescribing information for ATRIPLA.

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

Initial U.S. Approval: 2006

WARNINGS: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT EXACERBATION OF HEPATITIS B

See full prescribing information for complete boxed warning.

- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including tenofovir disoproxil fumarate, a component of ATRIPLA. (5.1)**
- **ATRIPLA is not approved for the treatment of chronic hepatitis B virus (HBV) infection. Severe acute exacerbations of hepatitis B have been reported in patients coinfected with HBV and HIV-1 who have discontinued EMTRIVA or VIREAD, two of the components of ATRIPLA. Hepatic function should be monitored closely in these patients. If appropriate, initiation of anti-hepatitis B therapy may be warranted. (5.2)**

RECENT MAJOR CHANGES

Boxed Warning	1/2010
Warnings and Precautions	
Patients Coinfected with HIV-1 and HBV (5.2)	1/2010
New Onset or Worsening Renal Impairment (5.7)	1/2010
Reproductive Risk Potential (5.8)	1/2010
Decrease in Bone Mineral Density (5.11)	1/2010

INDICATIONS AND USAGE

ATRIPLA, a combination of 2 nucleoside analog HIV-1 reverse transcriptase inhibitors and 1 non-nucleoside HIV-1 reverse transcriptase inhibitor, 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. (1)

DOSAGE AND ADMINISTRATION

- Recommended dose: One tablet once daily taken orally on an empty stomach, preferably at bedtime. (2)
- Dose in renal impairment: Should not be administered in patients with creatinine clearance <50 mL/min. (2)

DOSAGE FORMS AND STRENGTHS

Tablet containing 600 mg of efavirenz, 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate. (3)

CONTRAINDICATIONS

- Previously demonstrated hypersensitivity (e.g., Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to efavirenz, a component of ATRIPLA. (4.1)
- For some drugs, competition for CYP3A by efavirenz could result in inhibition of their metabolism and create the potential for serious and/or life-threatening adverse reactions (e.g., cardiac arrhythmias, prolonged sedation, or respiratory depression). (4.2)

WARNINGS AND PRECAUTIONS

- Serious psychiatric symptoms: Immediate medical evaluation is recommended. (5.5, 6.1)
- Nervous system symptoms (NSS): NSS are frequent, usually begin 1-2 days after initiating therapy and resolve in 2-4 weeks. Dosing at bedtime may improve tolerability. NSS are not predictive of onset of psychiatric symptoms. (2, 5.6)
- New onset or worsening renal impairment: Can include acute renal failure and Fanconi syndrome. Assess creatinine clearance (CrCl) before initiating treatment with ATRIPLA. Monitor CrCl and serum phosphorus in patients at risk. Avoid administering ATRIPLA with concurrent or recent use of nephrotoxic drugs. (5.7)
- Pregnancy: Fetal harm can occur when administered to a pregnant woman during the first trimester. Women should be apprised of the potential harm to the fetus. (5.8)
- Rash: Discontinue if severe rash develops. (5.9, 6.1)
- Hepatotoxicity: Monitor liver function tests before and during treatment in patients with underlying hepatic disease, including hepatitis B and C, or marked transaminase elevations. (5.10, 8.6)
- Decreases in bone mineral density (BMD): Consider monitoring BMD in patients with a history of pathological fracture or who are at risk for osteopenia. (5.11)
- Convulsions: Use caution in patients with a history of seizures. (5.12)
- Immune reconstitution syndrome: May necessitate further evaluation and treatment. (5.13)
- Redistribution/accumulation of body fat: Observed in patients receiving antiretroviral therapy. (5.14)
- Coadministration with other products: Do not use with drugs containing efavirenz, emtricitabine or tenofovir disoproxil fumarate including SUSTIVA, TRUVADA, EMTRIVA, VIREAD; or with drugs containing lamivudine. Do not administer in combination with HEPSERA. (5.4)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥10%) observed in an active-controlled clinical study of efavirenz, emtricitabine, and tenofovir DF are diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at 1-800-GILEAD-5 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Efavirenz: Coadministration of efavirenz can alter the concentrations of other drugs and other drugs may alter the concentrations of efavirenz. The potential for drug-drug interactions must be considered before and during therapy. (4.2, 7.1, 12.3)
- Didanosine: Tenofovir disoproxil fumarate increases didanosine concentrations. Use with caution and monitor for evidence of didanosine toxicity (e.g., pancreatitis, neuropathy) when coadministered. Consider dose reductions or discontinuations of didanosine if warranted. (7.2)
- Atazanavir: Coadministration of ATRIPLA and atazanavir or atazanavir/ritonavir is not recommended. (7.3)
- Lopinavir/ritonavir: Coadministration increases tenofovir concentrations. Monitor for evidence of tenofovir toxicity. (7.3)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Women should avoid pregnancy while receiving ATRIPLA and for 12 weeks after discontinuation. (5.8)
- Nursing mothers: Women infected with HIV should be instructed not to breast feed. (8.3)
- Hepatitis B or C coinfection or therapy with medications associated with liver toxicity: Use caution in patients with hepatic impairment. (5.10, 6.2, 8.6)

- Pediatrics: Safety and efficacy not established in patients less than 18 years of age. (2, 8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNINGS: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT EXACERBATION OF HEPATITIS B

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

4.1 Hypersensitivity

4.2 Contraindicated Drugs

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis/Severe Hepatomegaly with Steatosis

5.2 Patients Coinfected with HIV-1 and HBV

5.3 Drug Interactions

5.4 Coadministration with Related Products

5.5 Psychiatric Symptoms

5.6 Nervous System Symptoms

5.7 New Onset or Worsening Renal Impairment

5.8 Reproductive Risk Potential

5.9 Rash

5.10 Liver Enzymes

5.11 Decreases in Bone Mineral Density

5.12 Convulsions

5.13 Immune Reconstitution Syndrome

5.14 Fat Redistribution

6 ADVERSE REACTIONS

6.1 Adverse Reactions from Clinical Trials Experience

6.2 Laboratory Abnormalities

6.3 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Efavirenz

7.2 Emtricitabine and Tenofovir Disoproxil Fumarate

7.3 Efavirenz, Emtricitabine and Tenofovir Disoproxil Fumarate

7.4 Efavirenz Assay Interference

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Hepatic Impairment

8.7 Renal Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.3 Pharmacokinetics

12.4 Microbiology

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION and FDA-APPROVED PATIENT LABELING

17.1 Drug Interactions

17.2 General Information

17.3 Lactic Acidosis/Severe Hepatomegaly with Steatosis

17.4 Patients Coinfected with HIV-1 and HBV

17.5 New Onset or Worsening Renal Impairment

17.6 Decreases in Bone Mineral Density

17.7 Dosing Instructions

17.8 Nervous System Symptoms

17.9 Psychiatric Symptoms

17.10 Rash

17.11 Reproductive Risk Potential

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNINGS: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT EXACERBATION OF HEPATITIS B

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including tenofovir disoproxil fumarate, a component of ATRIPLA, in combination with other antiretrovirals *[See Warnings and Precautions (5.1)]*.

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-1. Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued EMTRIVA or VIREAD, which are components of ATRIPLA. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue ATRIPLA. If appropriate, initiation of anti-hepatitis B therapy may be warranted *[See Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

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

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

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

4.1 Hypersensitivity

ATRIPLA is contraindicated in patients with previously demonstrated clinically significant hypersensitivity (e.g., Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to efavirenz, a component of ATRIPLA.

4.2 Contraindicated Drugs

For some drugs, competition for CYP3A by efavirenz could result in inhibition of their metabolism and create the potential for serious and/or life-threatening adverse reactions (e.g., cardiac arrhythmias, prolonged sedation, or respiratory depression). Drugs that are contraindicated with ATRIPLA are listed in Table 1.

Table 1 Drugs That Are Contraindicated or Not Recommended for Use With ATRIPLA

Drug Class: Drug Name	Clinical Comment
Antifungal: voriconazole	Efavirenz significantly decreases voriconazole plasma concentrations, and coadministration may decrease the therapeutic effectiveness of voriconazole. Also, voriconazole significantly increases efavirenz plasma concentrations, which may increase the risk of efavirenz-associated side effects. Because ATRIPLA is a fixed-dose combination product, the dose of efavirenz cannot be altered. *[See Clinical Pharmacology (12.3) Tables 5 and 6]*
Ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine)	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	Potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.
Calcium channel blocker: bepridil	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
GI motility agent: cisapride	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Neuroleptic: pimozide	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
St. John's wort (*Hypericum perforatum*)	May lead to loss of virologic response and possible resistance to efavirenz or to the class of non-nucleoside reverse transcriptase inhibitors (NNRTIs).

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs including tenofovir DF, a component of ATRIPLA, in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with ATRIPLA should be

suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

5.2 Patients Coinfected with HIV-1 and HBV

It is recommended that all patients with HIV-1 be tested for the presence of chronic 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 coinfected with HBV and HIV-1. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued emtricitabine or tenofovir DF, two of the components of ATRIPLA. In some patients infected with HBV and treated with emtricitabine, the exacerbations of hepatitis B were associated with liver decompensation and liver failure. Patients who are coinfected with HIV-1 and HBV should be closely monitored with both clinical and laboratory follow up for at least several months after stopping treatment with ATRIPLA. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

ATRIPLA should not be administered with HEPSERA® (adefovir dipivoxil) *[See Drug Interactions (7.2)]*.

5.3 Drug Interactions

Efavirenz plasma concentrations may be altered by substrates, inhibitors, or inducers of CYP3A. Likewise, efavirenz may alter plasma concentrations of drugs metabolized by CYP3A *[See Contraindications (4.2), Drug Interactions (7.1)]*.

5.4 Coadministration with Related Products

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

5.5 Psychiatric Symptoms

Serious psychiatric adverse experiences have been reported in patients treated with efavirenz. In controlled trials of 1008 subjects treated with regimens containing efavirenz for a mean of 2.1 years and 635 subjects treated with control regimens for a mean of 1.5 years, the frequency (regardless of causality) of specific serious psychiatric events among subjects who received efavirenz or control regimens, respectively, were: severe depression (2.4%, 0.9%), suicidal ideation (0.7%, 0.3%), nonfatal suicide attempts (0.5%, 0%), aggressive behavior (0.4%, 0.5%), paranoid reactions (0.4%, 0.3%), and manic reactions (0.2%, 0.3%). When psychiatric symptoms similar to those noted above were combined and evaluated as a group in a multifactorial analysis of data from Study AI266006 (006), treatment with efavirenz was associated with an increase in the occurrence of these selected psychiatric symptoms. Other factors associated with an increase in the occurrence of these psychiatric symptoms were history of injection drug use, psychiatric history, and receipt of psychiatric medication at

study entry; similar associations were observed in both the efavirenz and control treatment groups. In Study 006, onset of new serious psychiatric symptoms occurred throughout the study for both efavirenz-treated and control-treated subjects. One percent of efavirenz-treated subjects 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, and psychosis-like behavior, although a causal relationship to the use of efavirenz cannot be determined from these reports. Patients with serious psychiatric adverse experiences should seek immediate medical evaluation to assess the possibility that the symptoms may be related to the use of efavirenz, and if so, to determine whether the risks of continued therapy outweigh the benefits *[See Adverse Reactions (6)]*.

5.6 Nervous System Symptoms

Fifty-three percent (531/1008) of subjects receiving efavirenz in controlled trials reported central nervous system symptoms (any grade, regardless of causality) compared to 25% (156/635) of subjects receiving control regimens. These symptoms included dizziness (28.1% of the 1008 subjects), 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 subjects. Overall, 2.1% of subjects discontinued therapy as a result. These symptoms usually begin during the first or second day of therapy and generally resolve after the first 2–4 weeks of therapy. After 4 weeks of therapy, the prevalence of nervous system symptoms of at least moderate severity ranged from 5% to 9% in subjects treated with regimens containing efavirenz and from 3% to 5% in subjects treated with a control regimen. Patients should be informed that these common symptoms were likely to improve with continued therapy and were not predictive of subsequent onset of the less frequent psychiatric symptoms *[See Warnings and Precautions (5.5)]*. Dosing at bedtime may improve the tolerability of these nervous system symptoms *[See Dosage and Administration (2)]*.

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

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

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

5.7 New Onset or Worsening Renal Impairment

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

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir DF *[See Adverse Reactions (6.3)].*

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

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

5.8 Reproductive Risk Potential

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

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

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

Efavirenz: As of July 2008, the Antiretroviral Pregnancy Registry has received prospective reports of 526 pregnancies exposed to efavirenz-containing regimens, nearly all of which were first-trimester exposures (507 pregnancies). Birth defects occurred in 13 of 407 live births (first-trimester exposure) and 2 of 37 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 efavirenz has also been prospectively reported; however, this case included severe oblique facial clefts and amniotic banding, a known association with anophthalmia. There have been five retrospective reports of findings consistent with neural tube defects, including meningomyelocele. All mothers were exposed to efavirenz-containing regimens in the first trimester. Although a causal relationship of these events to the use of efavirenz has not been established, similar defects have been observed in preclinical studies of efavirenz.

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

5.9 Rash

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

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

5.10 Liver Enzymes

In patients with known or suspected history of hepatitis B or C infection and in patients treated with other medications associated with liver toxicity, monitoring of liver enzymes is recommended *[See also Warnings and Precautions (5.2)]*. In patients with persistent elevations of serum transaminases to greater than five times the upper limit of the normal range, the benefit of continued therapy with ATRIPLA needs to be weighed against the unknown risks of significant liver toxicity *[See Adverse Reactions (6.2)]*.

5.11 Decreases in Bone Mineral Density

Bone mineral density (BMD) monitoring should be considered for HIV-1 infected subjects 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-naive subjects receiving tenofovir DF, decreases in 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 subjects receiving tenofovir DF + lamivudine + efavirenz compared with subjects receiving stavudine + lamivudine + efavirenz. Changes in BMD at the hip were similar between the two treatment groups. In both groups, the majority of the reduction in BMD occurred in the first 24–48 weeks of the study and this reduction was sustained through 144 weeks. Twenty-eight percent of tenofovir DF-treated subjects vs. 21% of the comparator subjects 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 subjects in the tenofovir DF group and 6 subjects in the comparator group. Tenofovir DF was associated with significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide, and urinary N-telopeptide), suggesting increased bone turnover. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in subjects receiving tenofovir DF. The effects of tenofovir DF-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. For additional information, consult the tenofovir DF prescribing information.

Cases of osteomalacia (associated with proximal renal tubulopathy and which may contribute to fractures) have been reported in association with the use of tenofovir DF *[See Adverse Reactions (6.3)]*.

5.12 Convulsions

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

Patients who are receiving concomitant anticonvulsant medications primarily metabolized by the liver, such as phenytoin and phenobarbital, may require periodic monitoring of plasma levels *[See Drug Interactions (7.3)]*.

5.13 Immune Reconstitution Syndrome

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

5.14 Fat Redistribution

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

6 ADVERSE REACTIONS

Efavirenz, Emtricitabine and Tenofovir Disoproxil Fumarate: The following adverse reactions are discussed in other sections of the labeling:

- Lactic Acidosis/Severe Hepatomegaly with Steatosis *[See Boxed Warning, Warnings and Precautions (5.1)].*
- Severe Acute Exacerbations of Hepatitis B *[See Boxed Warning, Warnings and Precautions (5.2)].*
- Psychiatric Symptoms *[See Warnings and Precautions (5.5)].*
- Nervous System Symptoms *[See Warnings and Precautions (5.6)].*
- New Onset or Worsening Renal Impairment *[See Warnings and Precautions (5.7)].*
- Rash *[See Warnings and Precautions (5.9)].*
- Decreases in Bone Mineral Density *[See Warnings and Precautions (5.11)].*
- Immune Reconstitution Syndrome *[See Warnings and Precautions (5.13)].*
- Drug Interactions *[See Contraindications (4.2), Warnings and Precautions (5.3) and Drug Interactions (7)].*

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

6.1 Adverse Reactions from Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Study 934

Study 934 was an open-label active-controlled study in which 511 antiretroviral-naive subjects received either emtricitabine + tenofovir DF administered in combination with efavirenz (N=257) or zidovudine/lamivudine administered in combination with efavirenz (N=254).

The most common adverse reactions (incidence ≥ 10%, any severity) occurring in Study 934 include diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash. Adverse reactions observed in Study 934 were generally consistent with those seen in previous studies of the individual components (Table 2).

Table 2 Selected Treatment-Emergent Adverse Reactions[a] (Grades 2–4) Reported in ≥5% in Either Treatment Group in Study 934 (0–144 Weeks)

	FTC + TDF + EFV[b]	AZT/3TC + EFV
	N=257	N=254
Gastrointestinal Disorder		
Diarrhea	9%	5%
Nausea	9%	7%
Vomiting	2%	5%
General Disorders and Administration Site Condition		
Fatigue	9%	8%
Infections and Infestations		
Sinusitis	8%	4%
Upper respiratory tract infections	8%	5%
Nasopharyngitis	5%	3%
Nervous System Disorders		
Headache	6%	5%
Dizziness	8%	7%
Psychiatric Disorders		
Anxiety	5%	4%
Depression	9%	7%
Insomnia	5%	7%
Skin and Subcutaneous Tissue Disorders		
Rash Event[c]	7%	9%

a. Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.

b. From Weeks 96 to 144 of the study, subjects received emtricitabine/tenofovir DF administered in combination with efavirenz in place of emtricitabine + tenofovir DF with efavirenz.

c. Rash event includes rash, exfoliative rash, rash generalized, rash macular, rash maculo-papular, rash pruritic, and rash vesicular.

Study 073

In Study 073, subjects 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 the individual components of ATRIPLA when each was administered in combination with other antiretroviral agents.

Efavirenz, Emtricitabine, or Tenofovir Disoproxil Fumarate

In addition to the adverse reactions in Study 934 and Study 073 the following adverse reactions were observed in clinical trials of efavirenz, emtricitabine, or tenofovir DF in combination with other antiretroviral agents.

Efavirenz: The most significant adverse reactions observed in subjects treated with efavirenz are nervous system symptoms *[See Warnings and Precautions (5.6)],* psychiatric symptoms *[See Warnings and Precautions (5.5)],* and rash *[See Warnings and Precautions (5.9)].*

Selected adverse reactions of moderate-severe intensity observed in ≥2% of efavirenz-treated subjects in two controlled clinical trials included pain, impaired concentration, abnormal dreams, somnolence, anorexia, dyspepsia, abdominal pain, nervousness, and pruritus.

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

Emtricitabine and Tenofovir Disoproxil Fumarate: Adverse reactions that occurred in at least 5% of treatment-experienced or treatment-naive subjects receiving emtricitabine or tenofovir DF with other antiretroviral agents in clinical trials include arthralgia, increased cough, dyspepsia, fever, myalgia, pain, abdominal pain, back pain, paresthesia, peripheral neuropathy (including peripheral neuritis and neuropathy), pneumonia, rhinitis and rash event (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash and allergic reaction).

Skin discoloration has been reported with higher frequency among emtricitabine-treated subjects; it was manifested by hyperpigmentation on the palms and/or soles and was generally mild and asymptomatic. The mechanism and clinical significance are unknown.

6.2 Laboratory Abnormalities

Efavirenz, Emtricitabine and Tenofovir Disoproxil Fumarate: Laboratory abnormalities observed in Study 934 were generally consistent with those seen in previous studies (Table 3).

Table 3 Significant Laboratory Abnormalities Reported in ≥1% of Subjects in Either Treatment Group in Study 934 (0–144 Weeks)

	FTC + TDF + EFV[a]	AZT/3TC + EFV
	N=257	N=254
Any ≥ Grade 3 Laboratory Abnormality	30%	26%
Fasting Cholesterol (>240 mg/dL)	22%	24%
Creatine Kinase (M: >990 U/L) (F: >845 U/L)	9%	7%
Serum Amylase (>175 U/L)	8%	4%
Alkaline Phosphatase (>550 U/L)	1%	0%
AST (M: >180 U/L) (F: >170 U/L)	3%	3%
ALT (M: >215 U/L) (F: >170 U/L)	2%	3%
Hemoglobin (<8.0 mg/dL)	0%	4%
Hyperglycemia (>250 mg/dL)	2%	1%
Hematuria (>75 RBC/HPF)	3%	2%
Glycosuria (≥3+)	<1%	1%
Neutrophils (<750/mm^3)	3%	5%
Fasting Triglycerides (>750 mg/dL)	4%	2%

a. From Weeks 96 to 144 of the study, subjects received emtricitabine/tenofovir DF administered in combination with efavirenz in place of emtricitabine + tenofovir DF with efavirenz.

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

In addition to the laboratory abnormalities described for Study 934 (Table 3), Grade 3/4 elevations of bilirubin (>2.5 x ULN), pancreatic amylase (>2.0 x ULN), serum glucose (<40 or >250 mg/dL), and serum lipase (>2.0 x ULN) occurred in up to 3% of subjects treated with emtricitabine or tenofovir DF with other antiretroviral agents in clinical trials.

Hepatic Events: In Study 934, 19 subjects treated with efavirenz, emtricitabine, and tenofovir DF and 20 subjects treated with efavirenz and fixed-dose zidovudine/lamivudine were hepatitis B surface antigen or hepatitis C antibody positive. Among these coinfected subjects, one subject (1/19) in the efavirenz, emtricitabine and tenofovir DF arm had elevations in transaminases to greater than five times ULN through 144 weeks. In the fixed-dose zidovudine/lamivudine arm, two subjects (2/20) had elevations in transaminases to greater than five times ULN through 144 weeks. No HBV and/or HCV coinfected subject discontinued from the study due to hepatobiliary disorders *[See Warnings and Precautions (5.10)]*.

6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of efavirenz, emtricitabine, or tenofovir DF. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Efavirenz:

Cardiac Disorders
Palpitations

Ear and Labyrinth Disorders
Tinnitus

Endocrine Disorders
Gynecomastia

Eye Disorders
Abnormal vision

Gastrointestinal Disorders
Constipation, malabsorption

General Disorders and Administration Site Conditions
Asthenia

Hepatobiliary Disorders
Hepatic enzyme increase, hepatic failure, hepatitis

Immune System Disorders
Allergic reactions

Metabolism and Nutrition Disorders

Redistribution/accumulation of body fat *[See Warnings and Precautions (5.14)]*, hypercholesterolemia, hypertriglyceridemia

Musculoskeletal and Connective Tissue Disorders
Arthralgia, myalgia, myopathy

Nervous System Disorders
Abnormal coordination, ataxia, cerebellar coordination and balance disturbances, convulsions, hypoesthesia, paresthesia, neuropathy, tremor

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

Respiratory, Thoracic and Mediastinal Disorders
Dyspnea

Skin and Subcutaneous Tissue Disorders
Flushing, erythema multiforme, photoallergic dermatitis, Stevens-Johnson syndrome

Emtricitabine: No postmarketing adverse reactions have been identified for inclusion in this section.

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

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

Skin and Subcutaneous Tissue Disorders
Rash

Musculoskeletal and Connective Tissue Disorders
Rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute 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 Administration Site Conditions
Asthenia

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia, hypokalemia, muscular weakness, myopathy, hypophosphatemia.

7 DRUG INTERACTIONS

This section describes clinically relevant drug interactions with ATRIPLA. Drug interaction studies are described elsewhere in the labeling [*see Clinical Pharmacology (12.3)*].

7.1 Efavirenz

Efavirenz has been shown in vivo to induce CYP3A. Other compounds that are substrates of CYP3A may have decreased plasma concentrations when coadministered with efavirenz. In vitro studies have demonstrated that efavirenz inhibits CYP2C9, 2C19, and 3A4 isozymes in the range of observed efavirenz plasma concentrations. Coadministration of efavirenz 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 that induce CYP3A activity (e.g., phenobarbital, rifampin, rifabutin) would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations.

7.2 Emtricitabine and Tenofovir Disoproxil Fumarate

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

Coadministration of tenofovir DF and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse reactions. Didanosine should be discontinued in patients who develop didanosine-associated adverse reactions [for didanosine dosing adjustment recommendations, see *Table 4].* Suppression of $CD4^+$ cell counts has been observed in patients receiving tenofovir DF with didanosine 400 mg daily.

Lopinavir/ritonavir has been shown to increase tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving lopinavir/ritonavir with ATRIPLA should be monitored for tenofovir-associated adverse reactions. ATRIPLA should be discontinued in patients who develop tenofovir-associated adverse reactions [*See Table 4*].

Coadministration of atazanavir with ATRIPLA is not recommended since coadministration of atazanavir with either efavirenz or tenofovir DF has been shown to decrease plasma concentrations of atazanavir. Also, atazanavir has been shown to increase tenofovir concentrations. There are insufficient data to support dosing recommendations for atazanavir or atazanavir/ritonavir in combination with ATRIPLA [*See Table 4*].

7.3 Efavirenz, Emtricitabine and Tenofovir Disoproxil Fumarate

Other important drug interaction information for ATRIPLA is summarized in Table 1 and Table 4. The drug interactions described are based on studies conducted with efavirenz, emtricitabine or tenofovir DF as individual agents or are potential drug interactions; no drug interaction studies have been conducted using ATRIPLA [for pharmacokinetics data see *Clinical Pharmacology (12.3)*, Tables 5-9]. The tables include potentially significant interactions, but are not all inclusive.

Table 4 Established and Other Potentially Significant[a] Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect	Clinical Comment
Antiretroviral agents		
Protease inhibitor: atazanavir	↓atazanavir concentration ↑ tenofovir concentration	Coadministration of atazanavir with ATRIPLA is not recommended. Coadministration of atazanavir with either efavirenz or tenofovir DF decreases plasma concentrations of atazanavir. The combined effect of efavirenz plus tenofovir DF on atazanavir plasma concentrations is not known. Also, atazanavir has been shown to increase tenofovir concentrations. There are insufficient data to support dosing recommendations for atazanavir or atazanavir/ritonavir in combination with ATRIPLA.
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 efavirenz, is not known. Increasing the indinavir dose to 1000 mg every 8 hours does not compensate for the increased indinavir metabolism due to efavirenz.
Protease inhibitor: lopinavir/ritonavir	↓ lopinavir concentration ↑ tenofovir concentration	A dose increase of lopinavir/ritonavir to 600/150 mg (3 tablets) twice daily may be considered when used in combination with efavirenz in treatment-experienced patients where decreased susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). **Patients should be monitored for tenofovir-associated adverse reactions. ATRIPLA should be discontinued in patients who develop tenofovir-associated adverse reactions**.
Protease inhibitor: ritonavir	↑ ritonavir concentration ↑ efavirenz concentration	When ritonavir 500 mg every 12 hours was coadministered with efavirenz 600 mg once daily, the combination was associated with a higher frequency of adverse clinical experiences (e.g., dizziness, nausea, paresthesia) and laboratory abnormalities (elevated liver enzymes). Monitoring of liver enzymes is recommended when ATRIPLA is used in combination with ritonavir.

Concomitant Drug Class: Drug Name	Effect	Clinical Comment
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 reactions, including pancreatitis and neuropathy. **In adults weighing >60 kg, the didanosine dose should be reduced to 250 mg if coadministered with ATRIPLA. Data are not available to recommend a dose adjustment of didanosine for patients weighing <60 kg. Coadministration of ATRIPLA and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse reactions. For additional information, please consult the Videx / Videx EC (didanosine) prescribing information.**
Other agents		
Anticoagulant: warfarin	↑ or ↓ warfarin concentration	Plasma concentrations and effects potentially increased or decreased by efavirenz.
Anticonvulsants: carbamazepine	↓ carbamazepine concentration ↓ efavirenz concentration	There are insufficient data to make a dose recommendation for ATRIPLA. Alternative anticonvulsant treatment should be used.
phenytoin phenobarbital	↓ anticonvulsant concentration ↓ efavirenz concentration	Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.
Antidepressant: sertraline	↓ sertraline concentration	Increases in sertraline dose should be guided by clinical response.

Concomitant Drug Class: Drug Name	Effect	Clinical Comment
Antifungals: itraconazole	↓ itraconazole concentration ↓ hydroxy-itraconazole concentration	Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered.
ketoconazole	↓ ketoconazole concentration	Drug interaction studies with ATRIPLA and ketoconazole have not been conducted. Efavirenz has the potential to decrease plasma concentrations of ketoconazole.
Anti-infective: clarithromycin	↓ clarithromycin concentration ↑ 14-OH metabolite concentration	Clinical significance unknown. In uninfected volunteers, 46% developed rash while receiving efavirenz and clarithromycin. No dose adjustment of ATRIPLA is recommended when given with clarithromycin. Alternatives to clarithromycin, such as azithromycin, should be considered. Other macrolide antibiotics, such as erythromycin, have not been studied in combination with ATRIPLA.
Antimycobacterial: rifabutin	↓ rifabutin concentration	Increase daily dose of rifabutin by 50%. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week.
Antimycobacterial: rifampin	↓ efavirenz concentration	Clinical significance of reduced efavirenz concentration is unknown. Dosing recommendations for concomitant use of ATRIPLA and rifampin have not been established.
Calcium channel blockers: diltiazem	↓ diltiazem concentration ↓ desacetyl diltiazem concentration ↓ N-monodes-methyl diltiazem concentration	Diltiazem dose adjustments should be guided by clinical response (refer to the prescribing information for diltiazem). No dose adjustment of ATRIPLA is necessary when administered with diltiazem.
Others (e.g., felodipine, nicardipine, nifedipine, verapamil)	↓ calcium channel blocker	No data are available on the potential interactions of efavirenz with other calcium channel blockers that are substrates of CYP3A. 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).
HMG-CoA reductase inhibitors: atorvastatin pravastatin simvastatin	↓ atorvastatin concentration ↓ pravastatin concentration ↓ simvastatin concentration	Plasma concentrations of atorvastatin, pravastatin, and simvastatin decreased with efavirenz. Consult the prescribing information for the HMG-CoA reductase inhibitor for guidance on individualizing the dose.

Concomitant Drug Class: Drug Name	Effect	Clinical Comment
Hormonal contraceptives:		
Oral: Ethinyl estradiol/Norgestimate	↓ active metabolites of norgestimate	A reliable method of barrier contraception must be used in addition to hormonal contraceptives. Efavirenz had no effect on ethinyl estradiol concentrations, but progestin levels (norelgestromin and levonorgestrel) were markedly decreased. No effect of ethinyl estradiol/norgestimate on efavirenz plasma concentrations was observed.
Implant: Etonogestrel	↓ etonogestrel	A reliable method of barrier contraception must be used in addition to hormonal contraceptives. The interaction between etonogestrel and efavirenz has not been studied. Decreased exposure of etonogestrel may be expected. There have been postmarketing reports of contraceptive failure with etonogestrel in efavirenz-exposed patients.
Immunosuppressants: Cyclosporine, tacrolimus, sirolimus, and others metabolized by CYP3A	↓ immuno-suppressant	Decreased exposure of the immunosuppressant may be expected due to CYP3A induction by efavirenz. These immunosuppressants are not anticipated to affect exposure of efavirenz. Dose adjustments of the immunosuppressant may be required. Close monitoring of immunosuppressant concentrations for at least 2 weeks (until stable concentrations are reached) is recommended when starting or stopping treatment with ATRIPLA.
Narcotic analgesic: methadone	↓ methadone concentration	Coadministration of efavirenz in HIV-1 infected individuals with a history of injection drug use resulted in decreased plasma levels of methadone and signs of opiate withdrawal. Methadone dose was increased by a mean of 22% to alleviate withdrawal symptoms. Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.

a. This table is not all inclusive.

7.4 Efavirenz Assay Interference

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[See Warnings and Precautions (5.8)]*

8.3 Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-1 infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV-1. Studies in rats have demonstrated that both efavirenz and tenofovir are secreted in milk. It is not known whether efavirenz, emtricitabine, or tenofovir is excreted in human milk. Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving ATRIPLA.**

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Hepatic Impairment

The pharmacokinetics of efavirenz have not been adequately studied in subjects with hepatic impairment. Because of the extensive cytochrome P450-mediated metabolism of efavirenz and limited clinical experience in patients with hepatic impairment, caution should be exercised in administering ATRIPLA to these patients *[See Warnings and Precautions (5.10)].*

8.7 Renal Impairment

Because ATRIPLA is a fixed-dose combination, it should not be prescribed for patients requiring dosage adjustment such as those with moderate or severe renal impairment (creatinine clearance <50 mL/min) *[See Warnings and Precautions (5.7)].*

10 OVERDOSAGE

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

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

Emtricitabine: Limited clinical experience is available at doses higher than the therapeutic dose of emtricitabine. In one clinical pharmacology study single doses of emtricitabine 1200 mg were administered to 11 subjects. No severe adverse reactions were reported.

Hemodialysis treatment removes approximately 30% of the emtricitabine dose over a 3-hour dialysis period starting within 1.5 hours of emtricitabine dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min). It is not known whether emtricitabine can be removed by peritoneal dialysis.

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

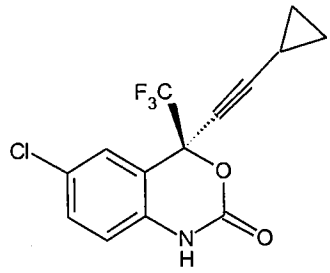
Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of tenofovir DF, a 4-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

11 DESCRIPTION

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

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

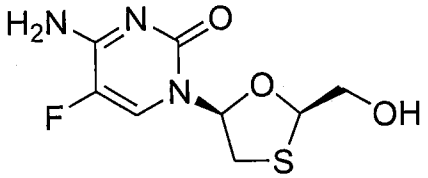
Efavirenz: Efavirenz is chemically described as (*S*)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2*H*-3,1-benzoxazin-2-one. Its molecular formula is $C_{14}H_9ClF_3NO_2$ and its structural formula is:



Efavirenz is a white to slightly pink crystalline powder with a molecular mass of 315.68. It is practically insoluble in water (<10 μg/mL).

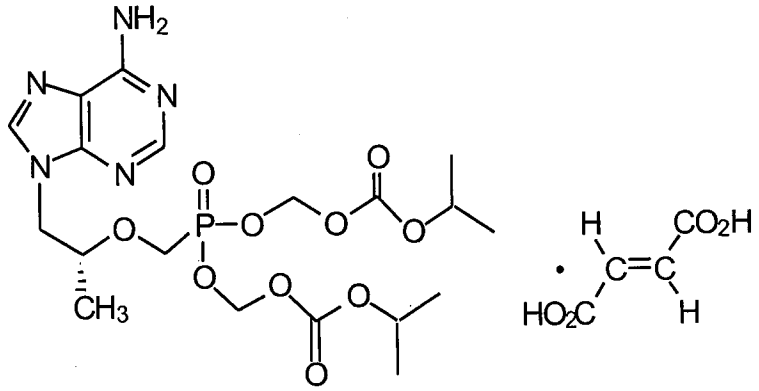
Emtricitabine: The chemical name of emtricitabine is 5-fluoro-1-(2*R*,5*S*)-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. Emtricitabine is the (-) enantiomer of a thio analog of cytidine, which differs from other cytidine analogs in that it has a fluorine in the 5-position.

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



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

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



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

12 CLINICAL PHARMACOLOGY

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

12.1 Mechanism of Action

ATRIPLA is a fixed-dose combination of antiviral drugs efavirenz, emtricitabine and tenofovir disoproxil fumarate. *[See Clinical Pharmacology (12.4)].*

12.3 Pharmacokinetics

ATRIPLA: One ATRIPLA tablet is 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-1 infected subjects time-to-peak plasma concentrations were approximately 3–5 hours and steady-state plasma concentrations were reached in 6–10 days. In 35 HIV-1 infected subjects receiving efavirenz 600 mg once daily, steady-state C_{max} was 12.9 ± 3.7 μM (mean ± SD), C_{min} was 5.6 ± 3.2 μM, and AUC was 184 ± 73 μM·hr. Efavirenz is highly bound (approximately 99.5–99.75%) to human plasma proteins, predominantly albumin. Following administration of ^{14}C-labeled efavirenz, 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 CYP3A and CYP2B6 are the major isozymes responsible for efavirenz metabolism. Efavirenz has been shown to induce CYP enzymes, resulting in induction of its own metabolism. Efavirenz has a terminal half-life of 52–76 hours after single doses and 40–55 hours after multiple doses.

Emtricitabine: Following oral administration, emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1–2 hours post-dose. Following multiple dose oral administration of emtricitabine to 20 HIV-1 infected subjects, the steady-state plasma emtricitabine C_{max} was 1.8 ± 0.7 μg/mL (mean ± SD) and the AUC over a 24-hour dosing interval was 10.0 ± 3.1 μg•hr/mL. The mean steady state plasma trough concentration at 24 hours post-dose was 0.09 μg/mL. The mean absolute bioavailability of emtricitabine was 93%. In vitro binding of emtricitabine to human plasma proteins is <4% and is independent of concentration over the range of 0.02–200 μg/mL. Following administration of radiolabelled emtricitabine, approximately 86% is recovered in the urine and 13% is recovered as metabolites. The metabolites of emtricitabine include 3′-sulfoxide diastereomers and their glucuronic acid conjugate. Emtricitabine is eliminated by a combination of glomerular filtration and active tubular secretion with a renal clearance in adults with normal renal function of 213 ± 89 mL/min (mean ± SD). Following a single oral dose, the plasma emtricitabine half-life is approximately 10 hours.

Tenofovir Disoproxil Fumarate: Following oral administration of a single 300 mg dose of tenofovir DF to HIV-1 infected subjects in the fasted state, maximum serum concentrations (C_{max}) were achieved in 1.0 ± 0.4 hrs (mean ± SD) and C_{max} and AUC values were 296 ± 90 ng/mL and 2287 ± 685 ng•hr/mL, respectively. The oral

bioavailability of tenofovir from tenofovir DF in fasted subjects is approximately 25%. In vitro binding of tenofovir to human plasma proteins is <0.7% and is independent of concentration over the range of 0.01–25 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 with a renal clearance in adults with normal renal function of 243 ± 33 mL/min (mean ± SD). Following a single oral dose, the terminal elimination half-life of tenofovir is approximately 17 hours.

Effects of Food on Oral Absorption

ATRIPLA has not been evaluated in the presence of food. Administration of efavirenz tablets with a high fat meal increased the mean AUC and C_{max} of efavirenz by 28% and 79%, respectively, compared to administration in the fasted state. Compared to fasted administration, dosing of tenofovir DF and emtricitabine in combination with either a high fat meal or a light meal increased the mean AUC and C_{max} of tenofovir by 35% and 15%, respectively, without affecting emtricitabine exposures *[See Dosage and Administration (2) and Patient Counseling Information (17.3)].*

Special Populations

Race

Efavirenz: The pharmacokinetics of efavirenz in HIV-1 infected subjects appear to be similar among the racial groups studied.

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

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

Gender

Efavirenz, Emtricitabine, and Tenofovir Disoproxil Fumarate: Efavirenz, emtricitabine, and tenofovir pharmacokinetics are similar in male and female subjects.

Pediatric and Geriatric Patients

Pharmacokinetic studies of tenofovir DF have not been performed in pediatric subjects (<18 years). Efavirenz has not been studied in pediatric subjects below 3 years of age or who weigh less than 13 kg. Emtricitabine has been studied in pediatric subjects from 3 months to 17 years of age. ATRIPLA is not recommended for pediatric administration. Pharmacokinetics of efavirenz, emtricitabine and tenofovir have not been fully evaluated in the elderly (>65 years) *[See Use in Specific Populations (8)].*

Patients with Impaired Renal Function

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

Emtricitabine and Tenofovir Disoproxil Fumarate: The pharmacokinetics of emtricitabine and tenofovir DF are altered in subjects with renal impairment. In subjects with creatinine clearance <50 mL/min, C_{max} and $AUC_{0-\infty}$ of emtricitabine and tenofovir were increased *[See Warnings and Precautions (5.7)]*.

Patients with Hepatic Impairment

Efavirenz: The pharmacokinetics of efavirenz have not been adequately studied in subjects with hepatic impairment *[See Warnings and Precautions (5.10) and Use in Specific Populations (8.6)]*.

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

Tenofovir Disoproxil Fumarate: The pharmacokinetics of tenofovir following a 300 mg dose of tenofovir DF have been studied in non-HIV infected subjects with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in subjects with hepatic impairment compared with unimpaired subjects.

Assessment of Drug Interactions

The drug interaction studies described were conducted with efavirenz, emtricitabine, or tenofovir DF as individual agents; no drug interaction studies have been conducted using ATRIPLA.

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

Efavirenz has been shown in vivo to cause hepatic enzyme induction, thus increasing the biotransformation of some drugs metabolized by CYP3A. In vitro studies have shown that efavirenz inhibited CYP isozymes 2C9, 2C19, and 3A4 with K_i values (8.5–17 μM) in the range of observed efavirenz plasma concentrations. In in vitro studies, efavirenz did not inhibit CYP2E1 and inhibited CYP2D6 and CYP1A2 (K_i values 82–160 μM) only at concentrations well above those achieved clinically. Coadministration of efavirenz with drugs primarily metabolized by 2C9, 2C19, and 3A4 isozymes may result in altered plasma concentrations of the coadministered drug. Drugs which induce CYP3A activity would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations.

Drug interaction studies were performed with efavirenz and other drugs likely to be coadministered or drugs commonly used as probes for pharmacokinetic interaction. There was no clinically significant interaction observed between efavirenz and zidovudine, lamivudine, azithromycin, fluconazole, lorazepam, cetirizine, or paroxetine. Single doses of famotidine or an aluminum and magnesium antacid with simethicone had no effects on efavirenz exposures. The effects of coadministration of efavirenz on C_{max}, AUC, and C_{min} are summarized in Table 5 (effect of other drugs on efavirenz) and

Table 6 (effect of efavirenz on other drugs). For information regarding clinical recommendations see *Drug Interactions (7).*

Table 5 **Drug Interactions: Changes in Pharmacokinetic Parameters for Efavirenz in the Presence of the Coadministered Drug**

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

				Mean % Change of Efavirenz Pharmacokinetic Parameters[a] (90% CI)		
Coadministered Drug	**Dose of Coadministered Drug (mg)**	**Efavirenz Dose (mg)**	**N**	**C_{max}**	**AUC**	**C_{min}**
Sertraline	50 mg qd × 14 days	600 mg × 14 days	13	↑ 11 (↑ 6 to ↑ 16)	↔	↔
Voriconazole	400 mg po q12h × 1 day then 200 mg po q12h × 8 days	400 mg × 9 days	NA	↑ 38[e]	↑ 44[e]	NA
	300 mg po q12h days 2-7	300 mg × 7 days	NA	↓ 14[f] (↓ 7 to ↓ 21)	↔[f]	NA
	400 mg po q12h days 2-7	300 mg × 7 days	NA	↔[f]	↑ 17[f] (↑ 6 to ↑ 29)	NA

NA = not available

a. Increase = ↑; Decrease = ↓; No Effect = ↔
b. Parallel-group design; N for efavirenz + lopinavir/ritonavir, N for efavirenz alone.
c. 95% CI
d. Soft Gelatin Capsule
e. 90% CI not available
f. Relative to steady-state administration of efavirenz (600 mg once daily for 9 days).

Table 6 Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Efavirenz

				Mean % Change of Coadministered Drug Pharmacokinetic Parameters[a] (90% CI)		
Coadministered Drug	**Dose of Coadministered Drug (mg)**	**Efavirenz Dose (mg)**	**N**	**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 (↓ 49 to ↓ 67)	↓ 74 (↓ 68 to ↓ 78)	↓ 93 (↓ 90 to ↓ 95)
	400 mg qd d 1–6, then 300 mg qd d 7–20 with ritonavir 100 mg qd and a light meal	600 mg qd 2 h after atazanavir and ritonavir d 7–20	13	↑ 14[b] (↓ 17 to ↑ 58)	↑ 39[b] (↑ 2 to ↑ 88)	↑ 48[b] (↑ 24 to ↑ 76)
	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 efavirenz)	600 mg qd with a light snack d 11-24 (pm)	14	↑ 17 (↑ 8 to ↑ 27)	↔	↓ 42 (↓ 31 to ↓ 51)

				Mean % Change of Coadministered Drug Pharmacokinetic Parameters[a] (90% CI)		
Coadministered Drug	**Dose of Coadministered Drug (mg)**	**Efavirenz Dose (mg)**	**N**	**C_{max}**	**AUC**	**C_{min}**
Indinavir	1000 mg q8h × 10 days	600 mg × 10 days	20			
	After morning dose			↔[c]	↓ 33[c] (↓ 26 to ↓ 39)	↓ 39[c] (↓ 24 to ↓ 51)
	After afternoon dose			↔[c]	↓ 37[c] (↓ 26 to ↓ 46)	↓ 52[c] (↓ 47 to ↓ 57)
	After evening dose			↓ 29[c] (↓ 11 to ↓ 43)	↓ 46[c] (↓ 37 to ↓ 54)	↓ 57[c] (↓ 50 to ↓ 63)
Lopinavir/ ritonavir	400/100 mg q12h × 9 days	600 mg × 9 days	11, 7[d]	↔[e]	↓ 19[e] (↓ 36 to ↑ 3)	↓ 39[e] (↓ 3 to ↓ 62)
Nelfinavir	750 mg q8h × 7 days	600 mg × 7 days	10	↑ 21 (↑ 10 to ↑ 33)	↑ 20 (↑ 8 to ↑ 34)	↔
Metabolite AG-1402				↓ 40 (↓ 30 to ↓ 48)	↓ 37 (↓ 25 to ↓ 48)	↓ 43 (↓ 21 to ↓ 59)
Ritonavir	500 mg q12h × 8 days	600 mg × 10 days	11			
	After AM dose			↑ 24 (↑ 12 to ↑ 38)	↑ 18 (↑ 6 to ↑ 33)	↑ 42 (↑ 9 to ↑ 86)[f]
	After PM dose			↔	↔	↑ 24 (↑ 3 to ↑ 50)[f]
Saquinavir SGC[g]	1200 mg q8h × 10 days	600 mg × 10 days	12	↓ 50 (↓ 28 to ↓ 66)	↓ 62 (↓ 45 to ↓ 74)	↓ 56 (↓ 16 to ↓ 77)[f]

				Mean % Change of Coadministered Drug Pharmacokinetic Parameters[a] (90% CI)		
Coadministered Drug	**Dose of Coadministered Drug (mg)**	**Efavirenz Dose (mg)**	**N**	**C_{max}**	**AUC**	**C_{min}**
Clarithromycin	500 mg q12h × 7 days	400 mg × 7 days	11	↓ 26 (↓ 15 to ↓ 35)	↓ 39 (↓ 30 to ↓ 46)	↓ 53 (↓ 42 to ↓ 63)
14-OH metabolite				↑ 49 (↑ 32 to ↑ 69)	↑ 34 (↑ 18 to ↑ 53)	↑ 26 (↑ 9 to ↑ 45)
Itraconazole	200 mg q12h × 28 days	600 mg ×14 days	18	↓ 37 (↓ 20 to ↓ 51)	↓ 39 (↓ 21 to ↓ 53)	↓ 44 (↓ 27 to ↓ 58)
Hydroxy-itraconazole				↓ 35 (↓ 12 to ↓ 52)	↓ 37 (↓ 14 to ↓ 55)	↓ 43 (↓ 18 to ↓ 60)
Rifabutin	300 mg qd × 14 days	600 mg × 14 days	9	↓ 32 (↓ 15 to ↓ 46)	↓ 38 (↓ 28 to ↓ 47)	↓ 45 (↓ 31 to ↓ 56)
Atorvastatin	10 mg qd × 4 days	600 mg × 15 days	14	↓ 14 (↓ 1 to ↓ 26)	↓ 43 (↓ 34 to ↓ 50)	↓ 69 (↓ 49 to ↓ 81)
Total active (including metabolites)				↓ 15 (↓ 2 to ↓ 26)	↓ 32 (↓ 21 to ↓ 41)	↓ 48 (↓ 23 to ↓ 64)
Pravastatin	40 mg qd × 4 days	600 mg × 15 days	13	↓ 32 (↓ 59 to ↑ 12)	↓ 44 (↓ 26 to ↓ 57)	↓ 19 (↓ 0 to ↓ 35)
Simvastatin	40 mg qd × 4 days	600 mg × 15 days	14	↓ 72 (↓ 63 to ↓ 79)	↓ 68 (↓ 62 to ↓ 73)	↓ 45 (↓ 20 to ↓ 62)
Total active (including metabolites)				↓ 68 (↓ 55 to ↓ 78)	↓ 60 (↓ 52 to ↓ 68)	NA[j]
Carbamazepine	200 mg qd × 3 days, 200 mg bid × 3 days, then 400 mg qd × 29 days	600 mg × 14 days	12	↓ 20 (↓ 15 to ↓ 24)	↓ 27 (↓ 20 to ↓ 33)	↓ 35 (↓ 24 to ↓ 44)
Epoxide metabolite				↔	↔	↓ 13 (↓ 30 to ↑ 7)
Diltiazem	240 mg × 21 days	600 mg × 14 days	13	↓ 60 (↓ 50 to ↓ 68)	↓ 69 (↓ 55 to ↓ 79)	↓ 63 (↓ 44 to ↓ 75)

				Mean % Change of Coadministered Drug Pharmacokinetic Parameters[a] (90% CI)		
Coadministered Drug	**Dose of Coadministered Drug (mg)**	**Efavirenz Dose (mg)**	**N**	**C_{max}**	**AUC**	**C_{min}**
Desacetyl diltiazem				↓ 64 (↓ 57 to ↓ 69)	↓ 75 (↓ 59 to ↓ 84)	↓ 62 (↓ 44 to ↓ 75)
N-monodesmethyl diltiazem				↓ 28 (↓ 7 to ↓ 44)	↓ 37 (↓ 17 to ↓ 52)	↓ 37 (↓ 17 to ↓ 52)
Ethinyl estradiol/ Norgestimate	0.035 mg/0.25 mg x 14 days	600 mg x 14 days				
Ethinyl estradiol			21	↔	↔	↔
Norelgestromin			21	↓ 46 (↓39 to ↓ 52)	↓ 64 (↓ 62 to ↓ 67)	↓ 82 (↓ 79 to ↓ 85)
Levonorgestrel			6	↓ 80 (↓77 to ↓ 83)	↓ 83 (↓79 to ↓ 87)	↓ 86 (↓80 to ↓ 90)
Methadone	Stable maintenance 35–100 mg daily	600 mg × 14–21 days	11	↓ 45 (↓ 25 to ↓ 59)	↓ 52 (↓ 33 to ↓ 66)	NA
Sertraline	50 mg qd × 14 days	600 mg × 14 days	13	↓ 29 (↓ 15 to ↓ 40)	↓ 39 (↓ 27 to ↓ 50)	↓ 46 (↓ 31 to ↓ 58)
Voriconazole	400 mg po q12h × 1 day then 200 mg po q12h x 8 days	400 mg × 9 days	NA	↓ 61[h]	↓ 77[h]	NA
	300 mg po q12h days 2-7	300 mg × 7 days	NA	↓ 36[i] (↓ 21 to ↓ 49)	↓ 55[i] (↓ 45 to ↓ 62)	NA
	400 mg po q12h days 2-7	300 mg × 7 days	NA	↑ 23[i] (↓ 1 to ↑ 53	↓ 7[i] (↓ 23 to ↑ 13)	NA

NA = not available

a. Increase = ↑; Decrease = ↓; No Effect = ↔
b. Compared with atazanavir 400 mg qd alone.
c. Comparator dose of indinavir was 800 mg q8h × 10 days.
d. Parallel-group design; N for efavirenz + lopinavir/ritonavir, N for lopinavir/ritonavir alone.
e. Values are for lopinavir. The pharmacokinetics of ritonavir 100 mg q12h are unaffected by concurrent efavirenz.
f. 95% CI
g Soft Gelatin Capsule

h. 90% CI not available
i. Relative to steady-state administration of voriconazole (400 mg for 1 day, then 200 mg po q12h for 2 days).
j. Not available because of insufficient data.

Emtricitabine and Tenofovir Disoproxil Fumarate: The steady-state pharmacokinetics of emtricitabine and tenofovir were unaffected when emtricitabine and tenofovir DF were administered together versus each agent dosed alone.

In vitro and clinical pharmacokinetic drug-drug interaction studies have shown that the potential for CYP mediated interactions involving emtricitabine 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; however, coadministration of emtricitabine and tenofovir DF with drugs that are eliminated by active tubular secretion may increase concentrations of emtricitabine, tenofovir, and/or the coadministered drug.

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

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

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

The effects of coadministered drugs on the C_{max}, AUC, and C_{min} of tenofovir are shown in Table 7. The effects of coadministration of tenofovir DF on C_{max}, AUC, and C_{min} of coadministered drugs are shown in Table 8 and Table 9.

Table 7 Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir in the Presence of the Coadministered Drug[a,b]

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

a. All interaction studies conducted in healthy volunteers.
b. Subjects received tenofovir DF 300 mg once daily.
c. Increase = ↑; Decrease = ↓; No Effect = ↔
d. Reyataz Prescribing Information

Table 8 Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Tenofovir Disoproxil Fumarate[a,b]

Coadministered Drug	Dose of Coadministered Drug (mg)	N	Mean % Change of Coadministered Drug Pharmacokinetic Parameters[c] (90% CI)		
			C_{max}	AUC	C_{min}
Atazanavir[d]	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[e] (↓ 42 to ↓ 3)	↓ 23[e] (↓ 46 to ↑ 10)
Lopinavir	Lopinavir/ritonavir 400/100 twice daily × 14 days	24	↔	↔	↔
Ritonavir	Lopinavir/ritonavir 400/100 twice daily × 14 days	24	↔	↔	↔

a. All interaction studies conducted in healthy volunteers.
b. Subjects received tenofovir DF 300 mg once daily.
c. Increase = ↑; Decrease = ↓; No Effect = ↔
d. Reyataz Prescribing Information
e. In HIV-infected patients, addition of tenofovir DF to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and C_{min} values of atazanavir that were 2.3- and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone.

Coadministration of tenofovir DF with didanosine results in changes in the pharmacokinetics of didanosine that may be of clinical significance. Table 9

summarizes the effects of tenofovir DF on the pharmacokinetics of didanosine. Concomitant dosing of tenofovir DF with didanosine buffered tablets or enteric-coated capsules significantly increases the C_{max} and AUC of didanosine. When didanosine 250 mg enteric-coated capsules were administered with tenofovir DF, systemic exposures of didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions. The mechanism of this interaction is unknown [for didanosine dosing adjustment recommendations see *Drug Interactions (7.3)*, Table 4].

Table 9 Drug Interactions: Changes in Pharmacokinetic Parameters for Didanosine in the Presence of Tenofovir Disoproxil Fumarate[a,b]

Didanosine Dose (mg)/Method of Administration[d]	Tenofovir DF Method of Administration[b,d]	N	Mean % Change (90% CI) vs. Didanosine 400 mg Alone, Fasted[c]	
			C_{max}	AUC
Buffered tablets				
400 once daily[e] × 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)

a. All interaction studies conducted in healthy volunteers.
b. Subjects received tenofovir DF 300 mg once daily.
c. Increase = ↑; Decrease = ↓; No Effect = ↔
d. Administration with food was with a light meal (~373 kcal, 20% fat).
e. Includes 4 subjects weighing <60 kg receiving ddI 250 mg.

12.4 Microbiology

Mechanism of Action

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

Emtricitabine: Emtricitabine, a synthetic nucleoside 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 polymerase α, β, ε, and mitochondrial DNA polymerase γ.

Tenofovir Disoproxil Fumarate: Tenofovir DF is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir DF requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 RT by competing with the natural substrate deoxyadenosine 5′-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Antiviral Activity

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

Efavirenz: The concentration of efavirenz inhibiting replication of wild-type laboratory adapted strains and clinical isolates in cell culture by 90–95% (EC_{90-95}) ranged from 1.7–25 nM in lymphoblastoid cell lines, peripheral blood mononuclear cells, and macrophage/monocyte cultures. Efavirenz demonstrated additive antiviral activity against HIV-1 in cell culture when combined with non-nucleoside reverse transcriptase inhibitors (NNRTIs) (delavirdine and nevirapine), nucleoside reverse transcriptase inhibitors (NRTIs) (abacavir, didanosine, lamivudine, stavudine, zalcitabine, and zidovudine), protease inhibitors (PIs) (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir), and the fusion inhibitor enfuvirtide. Efavirenz demonstrated additive to antagonistic antiviral activity in cell culture with atazanavir. Efavirenz demonstrated antiviral activity against clade B and most non-clade B isolates (subtypes A, AE, AG, C, D, F, G, J, and N), but had reduced antiviral activity against group O viruses. Efavirenz is not active against HIV-2.

Emtricitabine: The antiviral activity in cell culture of emtricitabine against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. The 50% effective concentration (EC_{50}) values for emtricitabine were in the range of 0.0013–0.64 μM (0.0003–0.158 μg/mL). In drug combination studies of emtricitabine with NRTIs (abacavir, lamivudine, stavudine, zalcitabine, and zidovudine), NNRTIs (delavirdine, efavirenz, and nevirapine), and PIs (amprenavir, nelfinavir, ritonavir, and saquinavir), additive to synergistic effects were observed. Emtricitabine displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 0.007–0.075 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. In drug combination studies of tenofovir with NRTIs (abacavir, didanosine, lamivudine, stavudine, zalcitabine, and

zidovudine), NNRTIs (delavirdine, efavirenz, and nevirapine), and PIs (amprenavir, indinavir, nelfinavir, ritonavir, and saquinavir), additive to synergistic effects were observed. Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G and O (EC_{50} values ranged from 0.5–2.2 μM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 1.6 μM to 5.5 μM).

Resistance

Efavirenz, Emtricitabine, and Tenofovir Disoproxil Fumarate: HIV-1 isolates with reduced susceptibility to the combination of emtricitabine and tenofovir have been selected in cell culture and in clinical studies. Genotypic analysis of these isolates identified the M184V/I and/or K65R amino acid substitutions in the viral RT.

In a clinical study of treatment-naive subjects *[Study 934,* see *Clinical Studies (14)]* resistance analysis was performed on HIV-1 isolates from all confirmed virologic failure subjects with >400 copies/mL of HIV-1 RNA at Week 144 or early discontinuations. Genotypic resistance to efavirenz, predominantly the K103N substitution, was the most common form of resistance that developed. Resistance to efavirenz occurred in 13/19 analyzed subjects in the emtricitabine + tenofovir DF group and in 21/29 analyzed subjects in the zidovudine/lamivudine fixed-dose combination group. The M184V amino acid substitution, associated with resistance to emtricitabine and lamivudine, was observed in 2/19 analyzed subject isolates in the emtricitabine + tenofovir DF group and in 10/29 analyzed subject isolates in the zidovudine/lamivudine group. Through 144 weeks of Study 934, no subjects developed a detectable K65R substitution in their HIV-1 as analyzed through standard genotypic analysis.

In a clinical study of treatment-naive subjects, isolates from 8/47 (17%) analyzed subjects receiving tenofovir DF 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 subjects, 14/304 (5%) of tenofovir DF treated subjects 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 substitution in the HIV-1 RT gene resulting in the K65R amino acid substitution.

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

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

Emtricitabine: Emtricitabine-resistant isolates of HIV-1 have been selected in cell culture and in clinical studies. Genotypic analysis of these isolates showed that the

reduced susceptibility to emtricitabine was associated with a substitution in the HIV-1 RT gene at codon 184 which resulted in an amino acid substitution of methionine by valine or isoleucine (M184V/I).

Tenofovir Disoproxil Fumarate: HIV-1 isolates with reduced susceptibility to tenofovir have been selected in cell culture. These viruses expressed a K65R substitution 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 cell culture by the combination of emtricitabine and tenofovir are also observed in some HIV-1 isolates from subjects failing treatment with tenofovir in combination with either lamivudine or emtricitabine, and either abacavir or didanosine. Therefore, cross-resistance among these drugs may occur in patients whose virus harbors either or both of these amino acid substitutions.

Efavirenz: Clinical isolates previously characterized as efavirenz-resistant were also phenotypically resistant in cell culture to delavirdine and nevirapine compared to baseline. Delavirdine- and/or nevirapine-resistant clinical viral isolates with NNRTI resistance-associated substitutions (A98G, L100I, K101E/P, K103N/S, V106A, Y181X, Y188X, G190X, P225H, F227L, or M230L) showed reduced susceptibility to efavirenz in cell culture. Greater than 90% of NRTI-resistant isolates tested in cell culture retained susceptibility to efavirenz.

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

Tenofovir Disoproxil Fumarate: The K65R substitution selected by tenofovir is also selected in some HIV-1 infected patients treated with abacavir, didanosine, or zalcitabine. HIV-1 isolates with the K65R substitution also showed reduced susceptibility to emtricitabine and lamivudine. Therefore, cross-resistance among these drugs may occur in patients whose virus harbors the K65R substitution. 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. Subjects whose virus expressed an L74V substitution without zidovudine resistance associated substitutions (N=8) had reduced response to VIREAD. Limited data are available for patients whose virus expressed a Y115F substitution (N=3), Q151M substitution (N=2), or T69 insertion (N=4), all of whom had a reduced response.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

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

Tenofovir Disoproxil Fumarate: Long-term oral carcinogenicity studies of tenofovir DF in mice and rats were carried out at exposures up to approximately 16 times (mice) and 5 times (rats) those observed in humans at the therapeutic dose for HIV-1 infection. At the high dose in female mice, liver adenomas were increased at exposures 16 times that in humans. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose.

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

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

13.2 Animal Toxicology and/or Pharmacology

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

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

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

14 CLINICAL STUDIES

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

Clinical Study 073 provides clinical experience in subjects with stable, virologic suppression and no history of virologic failure who switched from their current regimen to ATRIPLA.

In antiretroviral treatment-experienced patients, the use of ATRIPLA tablets may be considered for patients with HIV-1 strains that are expected to be susceptible to the components of ATRIPLA as assessed by treatment history or by genotypic or phenotypic testing *[See Clinical Pharmacology (12.4)]*.

Study 934: Data through 144 weeks are reported for Study 934, a randomized, open-label, active-controlled multicenter study comparing emtricitabine + tenofovir DF administered in combination with efavirenz versus zidovudine/lamivudine fixed-dose combination administered in combination with efavirenz in 511 antiretroviral-naive subjects. From weeks 96 to 144 of the study, subjects received emtricitabine/tenofovir

DF fixed-dose combination with efavirenz in place of emtricitabine + tenofovir DF with efavirenz. Subjects had a mean age of 38 years (range 18–80), 86% were male, 59% were Caucasian and 23% were Black. The mean baseline $CD4^+$ cell count was 245 cells/mm^3 (range 2–1191) and median baseline plasma HIV-1 RNA was 5.01 log_{10} copies/mL (range 3.56–6.54). Subjects were stratified by baseline $CD4^+$ cell count (< or ≥ 200 cells/mm^3) and 41% had $CD4^+$ cell counts <200 cells/mm^3. Fifty-one percent (51%) of subjects had baseline viral loads >100,000 copies/mL. Treatment outcomes through 48 and 144 weeks for those subjects who did not have efavirenz resistance at baseline (n=487) are presented in Table 10.

Table 10 Outcomes of Randomized Treatment at Weeks 48 and 144 (Study 934)

Outcomes	At Week 48		At Week 144	
	FTC + TDF +EFV (N=244)	AZT/3TC +EFV (N=243)	FTC + TDF +EFV (N=227)[a]	AZT/3TC +EFV (N=229)[a]
Responder[b]	84%	73%	71%	58%
Virologic failure[c]	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[d]	10%	14%	20%	22%

a. Subjects who were responders at Week 48 or Week 96 (HIV-1 RNA <400 copies/mL) but did not consent to continue study after Week 48 or Week 96 were excluded from analysis.

b. Subjects achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Weeks 48 and 144.

c. Includes confirmed viral rebound and failure to achieve confirmed HIV-1 RNA <400 copies/mL through Weeks 48 and 144.

d. Includes lost to follow-up, patient withdrawal, noncompliance, protocol violation and other reasons.

Through Week 48, 84% and 73% of subjects in the emtricitabine + tenofovir DF group and the zidovudine/lamivudine group, respectively, achieved and maintained HIV-1 RNA <400 copies/mL (71% and 58% through Week 144). The difference in the proportion of subjects who achieved and maintained HIV-1 RNA <400 copies/mL through 48 weeks largely results from the higher number of discontinuations due to adverse events and other reasons in the zidovudine/lamivudine group in this open-label study. In addition, 80% and 70% of subjects in the emtricitabine + tenofovir DF group and the zidovudine/lamivudine group, respectively, achieved and maintained HIV-1 RNA <50 copies/mL through Week 48 (64% and 56% through Week 144). The mean increase from baseline in $CD4^+$ cell count was 190 cells/mm^3 in the emtricitabine + tenofovir DF group and 158 cells/mm^3 in the zidovudine/lamivudine group at Week 48 (312 and 271 cells/mm^3 at Week 144).

Through 48 weeks, 7 subjects in the emtricitabine + tenofovir DF group and 5 subjects in the zidovudine/lamivudine group experienced a new CDC Class C event (10 and 6 subjects through 144 weeks).

Study 073: Study 073 was a 48-week open-label, randomized clinical trial in subjects with stable, virologic suppression on combination 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 (NNRTI).

To be enrolled, subjects were to have HIV-1 RNA <200 copies/mL for at least 12 weeks on their current regimen prior to study entry with no known HIV-1 substitutions conferring resistance to the components of ATRIPLA and no history of virologic failure.

The study compared the efficacy of switching to ATRIPLA or staying on the baseline antiretroviral regimen (SBR). Subjects were randomized in a 2:1 ratio to switch to ATRIPLA (N=203) or stay on SBR (N=97). Subjects 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 96% had HIV-1 RNA <50 copies/mL. The median time since onset of antiretroviral therapy was 3 years and 88% of subjects were receiving their first antiretroviral regimen at study enrollment.

At Week 48, 89% and 87% of subjects who switched to ATRIPLA maintained HIV RNA <200 copies/mL and <50 copies/mL, respectively, compared to 88% and 85% who remained on SBR; this difference was not statistically significant. No changes in CD4+ cell counts from baseline to Week 48 were observed in either treatment arm.

16 HOW SUPPLIED/STORAGE AND HANDLING

ATRIPLA tablets are pink, capsule-shaped, film-coated, debossed with "123" on one side and plain-faced on the other side. Each bottle contains 30 tablets (NDC 15584-0101-1) and silica gel desiccant, and is closed with a child-resistant closure.

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

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

17 PATIENT COUNSELING INFORMATION and FDA-APPROVED PATIENT LABELING

17.1 Drug Interactions

A statement to patients and healthcare providers is included on the product's bottle labels: *ALERT: Find out about medicines that should NOT be taken with ATRIPLA.* ATRIPLA may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription, nonprescription medication, or herbal products, particularly St. John's wort.

17.2 Information for Patients

Patients should be advised that:

- ATRIPLA is not a cure for HIV-1 infection and that they may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician when using ATRIPLA.
- The use of ATRIPLA has not been shown to reduce the risk of transmission of HIV-1 to others through sexual contact or blood contamination. Patients should be advised to continue to practice safer sex and to use latex or polyurethane condoms to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions or blood. Patients should be advised never to re-use or share needles.
- The long term effects of ATRIPLA are unknown.
- Redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known.
- ATRIPLA should not be coadministered with SUSTIVA, EMTRIVA, VIREAD, or TRUVADA, or drugs containing lamivudine, including Combivir, Epivir, Epivir-HBV, Epzicom, or Trizivir.
- ATRIPLA should not be administered with HEPSERA *[See Warnings and Precautions (5.2)]*.

17.3 Lactic Acidosis/Severe Hepatomegaly with Steatosis

Patients should be informed that lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Treatment will be suspended in any patients who develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity (including nausea, vomiting, unusual or unexpected stomach discomfort, and weakness) *[See Warnings and Precautions (5.1)]*.

17.4 Patients Coinfected with HIV-1 and HBV

Patients with HIV-1 should be tested for hepatitis B virus (HBV) before initiating antiretroviral therapy.

Patients should be advised that severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued EMTRIVA (emtricitabine) or VIREAD (tenofovir DF), which are components of ATRIPLA.

17.5 New Onset or Worsening Renal Impairment

Renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported. ATRIPLA should be avoided with concurrent or recent use of a nephrotoxic agent *[See Warnings and Precautions (5.7)]*.

17.6 Decreases in Bone Mineral Density

Patients should be informed that decreases in bone mineral density have been observed with the use of tenofovir DF. Bone mineral density monitoring may be

performed in patients who have a history of pathologic bone fracture or are at risk for osteopenia *[See Warnings and Precautions (5.11)]*.

17.7 Dosing Instructions

Patients should be advised to take ATRIPLA orally on an empty stomach and that it is important to take ATRIPLA on a regular dosing schedule to avoid missing doses.

17.8 Nervous System Symptoms

Patients should be informed that central nervous system symptoms (NSS) including dizziness, insomnia, impaired concentration, drowsiness, and abnormal dreams are commonly reported during the first weeks of therapy with efavirenz. Dosing at bedtime may improve the tolerability of these symptoms, which are likely to improve with continued therapy. Patients should be alerted to the potential for additive effects when ATRIPLA is used concomitantly with alcohol or psychoactive drugs. Patients should be instructed that if they experience NSS they should avoid potentially hazardous tasks such as driving or operating machinery *[See Warnings and Precautions (5.6), and Dosage and Administration (2)]*.

17.9 Psychiatric Symptoms

Patients should be informed that serious psychiatric symptoms including severe depression, suicide attempts, aggressive behavior, delusions, paranoia, and psychosis-like symptoms have been reported in patients receiving efavirenz. If they experience severe psychiatric adverse experiences they should seek immediate medical evaluation. Patients should be advised to inform their physician of any history of mental illness or substance abuse *[See Warnings and Precautions (5.5)]*.

17.10 Rash

Patients should be informed that a common side effect is rash. Rashes usually go away without any change in treatment. However, since rash may be serious, patients should be advised to contact their physician promptly if rash occurs.

17.11 Reproductive Risk Potential

Women receiving ATRIPLA should be instructed to avoid pregnancy *[See Warnings and Precautions (5.8)]*. A reliable form of barrier contraception must always be used in combination with other methods of contraception, including oral or other hormonal contraception. Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of ATRIPLA is recommended. Women should be advised to notify their physician if they become pregnant or plan to become pregnant while taking ATRIPLA. If this drug is used during the first trimester of pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential harm to the fetus.

FDA-Approved Patient Labeling

Patient Information

ATRIPLA® (uh TRIP luh) Tablets

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

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

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

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

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

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

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

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

- Your skin or the white part of your eyes turns yellow (jaundice).
- Your urine turns dark.
- Your bowel movements (stools) turn light in color.
- You don't feel like eating food for several days or longer.
- You feel sick to your stomach (nausea).

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

What is ATRIPLA?

ATRIPLA contains 3 medicines, SUSTIVA® (efavirenz), EMTRIVA® (emtricitabine) and VIREAD® (tenofovir disoproxil fumarate also called tenofovir DF) combined in one pill. EMTRIVA and VIREAD are HIV-1 (human immunodeficiency virus) nucleoside analog reverse transcriptase inhibitors (NRTIs) and SUSTIVA is an HIV-1 non-nucleoside analog reverse transcriptase inhibitor (NNRTI). VIREAD and EMTRIVA are the components of TRUVADA®. ATRIPLA can be used alone as a complete regimen, or in combination with other anti-HIV-1 medicines to treat people with HIV-1 infection. ATRIPLA is for adults age 18 and over. ATRIPLA has not been studied in children under age 18 or adults over age 65.

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 helps block HIV-1 reverse transcriptase, a viral chemical in your body (enzyme) that is needed for HIV-1 to multiply. ATRIPLA lowers the amount of HIV-1 in the blood (viral load). ATRIPLA may also help to increase the number of T cells ($CD4^+$ cells), allowing your immune system to improve. Lowering the amount of HIV-1 in the blood lowers the chance of death or infections that happen when your immune system is weak (opportunistic infections).

Does ATRIPLA cure HIV-1 or AIDS?

ATRIPLA does not cure HIV-1 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-1 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) infection. **It is very important that you see your healthcare provider regularly while taking ATRIPLA.**

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

ATRIPLA has not been shown to lower your chance of passing HIV-1 to other people through sexual contact, sharing needles, or being exposed to your blood.

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

Who should not take ATRIPLA?

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

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

What should I tell my healthcare provider before taking ATRIPLA?
Tell your healthcare provider if you:

- **Are pregnant or planning to become pregnant** (see "What should I avoid while taking ATRIPLA?").
- **Are breastfeeding** (see "What should I avoid while taking ATRIPLA?").
- **Have kidney problems or are undergoing kidney dialysis treatment.**
- **Have bone problems.**
- **Have liver problems, including hepatitis B virus infection.** Your healthcare provider may want to do tests to check your liver while you take ATRIPLA.
- **Have ever had mental illness or are using drugs or alcohol.**
- **Have ever had seizures or are taking medicine for seizures.**

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

ATRIPLA may change the effect of other medicines, including the ones for HIV-1, and may cause serious side effects. Your healthcare provider may change your other medicines or change their doses. Other medicines, including herbal products, may affect ATRIPLA. For this reason, **it is very important to** let all your healthcare providers and pharmacists know what medications, herbal supplements, or vitamins you are taking.

MEDICINES YOU SHOULD NOT TAKE WITH ATRIPLA

- The following medicines may cause serious and life-threatening side effects when taken with ATRIPLA. You should not take any of these medicines while taking ATRIPLA: Vascor (bepridil), Propulsid (cisapride), Versed (midazolam), Orap (pimozide), Halcion (triazolam), ergot medications (for example, Wigraine and Cafergot).
- ATRIPLA also should not be used with Combivir (lamivudine/zidovudine), EMTRIVA, Epivir, Epivir-HBV (lamivudine), Epzicom (abacavir sulfate/lamivudine), Trizivir (abacavir sulfate/lamivudine/zidovudine), SUSTIVA, TRUVADA, or VIREAD.
- Vfend (voriconazole) should not be taken with ATRIPLA since it may lose its effect or may increase the chance of having side effects from ATRIPLA.
- **Do not take St. John's wort (*Hypericum perforatum*), or products containing St. John's wort with ATRIPLA.** St. John's wort is an herbal product sold as a dietary supplement. Talk with your healthcare provider if you are taking or are planning to take St. John's wort. Taking St. John's wort may decrease ATRIPLA levels and lead to increased viral load and possible resistance to ATRIPLA or cross-resistance to other anti-HIV-1 drugs.
- ATRIPLA should not be used with HEPSERA® (adefovir dipivoxil).

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

- Fortovase, Invirase (saquinavir), Biaxin (clarithromycin); or Sporanox (itraconazole); **these medicines may need to be replaced with another medicine when taken with ATRIPLA.**
- Calcium channel blockers such as Cardizem or Tiazac (diltiazem), Covera HS or Isoptin (verapamil) and others; Crixivan (indinavir); the immunosuppressant medicines cyclosporine (Gengraf, Neoral, Sandimmune, and others), Prograf (tacrolimus), or Rapamune (sirolimus); Methadone; Mycobutin (rifabutin); Rifampin; cholesterol-lowering medicines such as Lipitor (atorvastatin), Pravachol (pravastatin sodium), and Zocor (simvastatin); or Zoloft (sertraline); **these medicines may need to have their dose changed when taken with ATRIPLA.**
- Videx, 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.
- Reyataz (atazanavir sulfate) or Kaletra (lopinavir/ritonavir); these medicines may increase the amount of tenofovir DF (a component of ATRIPLA) in your blood, which could result in more side effects. Reyataz is not recommended with ATRIPLA. **You may need to be monitored more carefully** if you are taking ATRIPLA and Kaletra together. Also, the dose of Kaletra may need to be changed.
- Medicine for seizures [for example, Dilantin (phenytoin), Tegretol (carbamazepine), or phenobarbital]; your healthcare provider may want to switch you to another medicine or check drug levels in your blood from time to time.

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

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

How should I take ATRIPLA?

- Take the exact amount of ATRIPLA your healthcare provider prescribes. Never change the dose on your own. Do not stop this medicine unless your healthcare provider tells you to stop.
- You should take ATRIPLA on an empty stomach.
- Swallow ATRIPLA with water.
- Taking ATRIPLA at bedtime may make some side effects less bothersome.
- Do not miss a dose of ATRIPLA. If you forget to take ATRIPLA, take the missed dose right away, unless it is almost time for your next dose. Do not double the next dose. Carry on with your regular dosing schedule. If you need help in planning the best times to take your medicine, ask your healthcare provider or pharmacist.
- If you believe you took more than the prescribed amount of ATRIPLA, contact your local poison control center or emergency room right away.
- Tell your healthcare provider if you start any new medicine or change how you take old ones. Your doses may need adjustment.
- When your ATRIPLA supply starts to run low, get more from your healthcare provider 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.
- Your healthcare provider may want to do blood tests to check for certain side effects while you take ATRIPLA.

What should I avoid while taking ATRIPLA?

- **Women should not become pregnant while taking ATRIPLA and for 12 weeks after stopping it.** Serious birth defects have been seen in the babies of animals and women treated with efavirenz (a component of ATRIPLA) during pregnancy. It is not known whether efavirenz caused these defects. **Tell your healthcare provider right away if you are pregnant.** Also talk with your healthcare provider if you want to become pregnant.
- Women should not rely only on hormone-based birth control, such as pills, injections, or implants, because ATRIPLA may make these contraceptives ineffective. Women must use a reliable form of barrier contraception, such as a

condom or diaphragm, even if they also use other methods of birth control. Efavirenz, a component of ATRIPLA, may remain in your blood for a time after therapy is stopped. Therefore, you should continue to use contraceptive measures for 12 weeks after you stop taking ATRIPLA.

- **Do not breast-feed if you are taking ATRIPLA.** The Centers for Disease Control and Prevention recommend that mothers with HIV not breast-feed because they can pass the HIV through their milk to the baby. Also, ATRIPLA may pass through breast milk and cause serious harm to the baby. Talk with your healthcare provider if you are breast-feeding. You should stop breast-feeding or may need to use a different medicine.
- Taking ATRIPLA with alcohol or other medicines causing similar side effects as ATRIPLA, such as drowsiness, may increase those side effects.
- Do not take any other medicines, including prescription and nonprescription medicines and herbal products, without checking with your healthcare provider.
- **Avoid doing things that can spread HIV-1 infection** since ATRIPLA does not stop you from passing the HIV-1 infection to others.

What are the possible side effects of ATRIPLA?
ATRIPLA may cause the following serious side effects:

- **Lactic acidosis** (buildup of an acid in the blood). Lactic acidosis can be a medical emergency and may need to be treated in the hospital. **Call your healthcare provider right away if you get signs of lactic acidosis.** (See "What is the most important information I should know about ATRIPLA?")
- **Serious liver problems (hepatotoxicity)**, with liver enlargement (hepatomegaly) and fat in the liver (steatosis). Call your healthcare provider right away if you get any signs of liver problems. (See "What is the most important information I should know about ATRIPLA?")
- **"Flare-ups" of hepatitis B virus (HBV) infection**, in which the disease suddenly returns in a worse way than before, can occur if you have HBV and you stop taking ATRIPLA. Your healthcare provider will monitor your condition for several months after stopping ATRIPLA if you have both HIV-1 and HBV infection and may recommend treatment for your HBV. ATRIPLA is not approved for the treatment of hepatitis B virus infection. If you have advanced liver disease and stop treatment with ATRIPLA, the "flare-up" of hepatitis B may cause your liver function to decline.
- **Serious psychiatric problems.** A small number of patients may experience severe depression, strange thoughts, or angry behavior while taking ATRIPLA. Some patients have thoughts of suicide and a few have actually committed suicide. These problems may occur more often in patients who have had mental illness. Contact your healthcare provider right away if you think you are having these psychiatric symptoms, so your healthcare provider can decide if you should continue to take ATRIPLA.
- **Kidney problems** (including decline or failure of kidney function). If you have had kidney problems in the past or take other medicines that can cause kidney problems,

your healthcare provider should do regular blood tests to check your kidneys. Symptoms that may be related to kidney problems include a high volume of urine, thirst, muscle pain, and muscle weakness.

- **Changes in bone mineral density (thinning bones).** Laboratory tests show changes in the bones of patients treated with tenofovir DF, a component of ATRIPLA. Some HIV patients treated with tenofovir DF developed thinning of the bones (osteopenia) which could lead to fractures. If you have had bone problems in the past, your healthcare provider may need to do tests to check your bone mineral density or may prescribe medicines to help your bone mineral density. Additionally, bone pain and softening of the bone (which may contribute to fractures) may occur as a consequence of kidney problems.

Common side effects:

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

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

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

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

Other possible side effects with ATRIPLA:

- Changes in body fat. Changes in body fat develop in some patients taking anti HIV-1 medicine. These changes may include an increased amount of fat in the upper back and neck ("buffalo hump"), in the breasts, 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 fat changes are not known.
- Skin discoloration (small spots or freckles) may also happen with ATRIPLA.
- In some patients with advanced HIV infection (AIDS), signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor immediately.

- Additional side effects are inflammation of the pancreas, allergic reaction (including swelling of the face, lips, tongue, or throat), shortness of breath, pain, stomach pain, weakness and indigestion.

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

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

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

How do I store ATRIPLA?

- **Keep ATRIPLA and all other medicines out of reach of children.**
- Store ATRIPLA at room temperature 77 °F (25 °C).
- Keep ATRIPLA in its original container and keep the container tightly closed.
- 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.

General information about ATRIPLA:

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

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

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

What are the ingredients of ATRIPLA?

Active Ingredients: efavirenz, emtricitabine, and tenofovir disoproxil fumarate

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

℞ Only

January 2010

ATRIPLA is a trademark of Bristol-Myers Squibb & Gilead Sciences, LLC. EMTRIVA, TRUVADA, HEPSERA and VIREAD are trademarks of Gilead Sciences, Inc. SUSTIVA is a trademark of Bristol-Myers Squibb Pharma Company. Reyataz and Videx are

trademarks of Bristol-Myers Squibb Company. Pravachol is a trademark of ER Squibb & Sons, LLC. Other brands listed are the trademarks of their respective owners.

21-937-GS-006 January 2010