HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use efavirenz, lamivudine and tenofovir disoproxil fumarate safely and effectively. See full prescribing information for efavirenz, lamivudine and tenofovir disoproxil fumarate tablets.

Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, 600 mg/300 mg/300 mg

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

See full prescribing information for complete boxed warning.

- **Lactic acidosis and hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues including lamivudine and tenofovir disoproxil fumarate. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur. (5.1)**
- **Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine and tenofovir disoproxil fumarate. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.2)**

----------INDICATIONS AND USAGE----------

Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, a combination of one non-nucleoside reverse transcriptase inhibitor (efavirenz) and two nucleo(t)side reverse transcriptase inhibitors (lamivudine and tenofovir disoproxil fumarate), are indicated alone or in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and adolescents aged > 16 years and weighing at least 40 kg. (1)

----------DOSAGE AND ADMINISTRATION----------

- Recommended dose: One tablet (containing 600 mg of efavirenz, 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate) taken once daily orally on an empty stomach, preferably at bedtime. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 600 mg efavirenz, 300 mg lamivudine and 300 mg tenofovir disoproxil fumarate. (3)

----------CONTRAINDICATIONS----------

- Efavirenz, Lamivudine and Tenofovir disoproxil fumarate tablets are contraindicated in patients with previously demonstrated and clinically significant hypersensitivity (eg, Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the components of this product. (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 (eg, cardiac arrhythmias, prolonged sedation, or respiratory depression). (4.2)

----------WARNINGS AND PRECAUTIONS----------

- Lactic acidosis and severe hepatomegaly with steatosis: Reported with the use of nucleoside analogues. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur. (5.1)
- Severe acute exacerbations of hepatitis B: Reported in patients who are co-infected with hepatitis B virus and HIV-1 and have discontinued lamivudine or tenofovir disoproxil fumarate. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.2)
- Coadministration with Other Products: Do not use with other efavirenz, lamivudine or tenofovir containing products or emtricitabine-containing products. Do not administer in combination with adefovir dipivoxil. (5.3)
- Hepatic decompensation, some fatal, has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy and interferon and ribavirin-based regimens. Monitor for treatment-associated toxicities. Discontinue Efavirenz, Lamivudine and Tenofovir disoproxil fumarate, as medically appropriate and consider dose reduction or discontinuation of interferon alfa, ribavirin, or both. (5.4)
- Pancreatitis: Use with caution in pediatric patients with a history of pancreatitis or other significant risk factors for pancreatitis. Discontinue Efavirenz, Lamivudine and Tenofovir disoproxil fumarate as clinically appropriate. (5.5)
- New onset or worsening renal impairment: Can include acute renal failure and Fanconi syndrome. Assess estimated creatinine clearance before initiating treatment with tenofovir disoproxil fumarate, a component of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate. In patients at risk for renal dysfunction, assess estimated creatinine clearance, serum phosphorus, urine glucose and urine protein before initiating treatment with tenofovir and periodically during treatment. Avoid administering efavirenz, lamivudine and tenofovir disoproxil fumarate with concurrent or recent use of nephrotoxic drugs. (5.6)
- Serious psychiatric symptoms: Immediate medical evaluation is recommended for serious psychiatric symptoms such as severe depression or suicidal ideation.(5.7, 17.1)
- Nervous system symptoms (NSS): NSS are frequent, usually begin 1 to 2 days after initiating therapy and resolve in 2 to 4 weeks. Dosing at bedtime may improve tolerability. NSS are not predictive of onset of psychiatric symptoms. (5.8, 17.1)
- 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. (5.9, 17.1) Pregnancy registry is available (8.1)
- Hepatotoxicity: Monitor liver function tests before and during treatment in patients with underlying hepatic disease, including hepatitis B or C coinfection, marked transaminase elevations, or who are taking medications associated with liver toxicity. Among reported cases of hepatic failure, a few occurred in patients with no pre-existing hepatic disease. (5.11, 8.7)
- Rash: Rash usually begins within 1 to 2 weeks after initiating therapy and resolves within 4 weeks. Discontinue if severe rash develops. (5.10, 17.1)
- Convulsions: Use caution in patients with a history of seizures. (5.12)
- Lipids: Total cholesterol and triglyceride elevations. Monitor before therapy and periodically thereafter. (5.13)
- Decreases in bone mineral density (BMD): Observed in HIV-infected patients. Consider assessment of BMD in patients with a history of pathologic fracture or other risk factors for osteoporosis or bone loss. (5.14)
- Immune reconstitution syndrome: Observed in HIV-infected patients. May necessitate further evaluation and treatment. (5.15)
- Redistribution/accumulation of body fat: Observed in HIV-infected patients receiving antiretroviral combination therapy. (5.16)

----------ADVERSE REACTIONS----------

- Most common adverse reactions are headache, nausea, malaise and fatigue, nasal signs and symptoms, diarrhea, rash, dizziness, insomnia, pain, depression, asthenia, and cough. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Cipla Ltd. at 1-866-604-3268 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Didanosine: Coadministration 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. (7.5)
- HIV-1 protease inhibitors: Coadministration decreases atazanavir concentrations and increases tenofovir concentrations. When coadministered with tenofovir, use atazanavir given with ritonavir; monitor for evidence of tenofovir toxicity. (7.6)
- Coadministration of tenofovir with atazanavir and ritonavir, darunavir and ritonavir, or lopinavir/ritonavir increases tenofovir concentrations. Monitor for evidence of tenofovir toxicity. (7.6)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Women should avoid pregnancy during efavirenz therapy, a component of Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate, and for 12 weeks after discontinuation. (5.9)
- Nursing mothers: Women infected with HIV should be instructed not to breast-feed. (8.3)

- Hepatic impairment: Efavirenz is not recommended for patients with moderate or severe hepatic impairment. Use caution in patients with mild hepatic impairment. (8.7)
- Pediatric patients: The incidence of rash was higher than in adults. (5.10, 6.1, 8.4)

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

Revised: 08/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*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 ACUTE EXACERBATIONS OF HEPATITIS B

Lactic acidosis and hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues including lamivudine and tenofovir disoproxil fumarate. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur *[See Warnings and Precautions (5.1)]*.

Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine and tenofovir disoproxil fumarate. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment *[See Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

Efavirenz, Lamivudine and Tenofovir disoproxil fumarate is indicated alone or in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and adolescents aged > 16 years weighing at least 40 kg.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose in Adults and Adolescents aged > 16 years (weighing at least 40 kg)

The recommended dose of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate (containing 600 mg of efavirenz, 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate) is one tablet per day taken orally on an empty stomach, preferably at bedtime.

2.2 Dose Adjustment for Renal Impairment

Because Efavirenz, Lamivudine and Tenofovir disoproxil fumarate is a fixed-dose combination tablet, it is not recommended for patients with impaired renal function (creatinine clearance less than 50 mL/min) or patients with end-stage renal disease (ESRD) requiring hemodialysis.

3 DOSAGE FORMS AND STRENGTHS

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets contains 600 mg of Efavirenz, 300 mg of Lamivudine and 300 mg tenofovir disoproxil fumarate. Yellow coloured, capsule shaped, biconvex, film coated tablets with “T” debossed on one side & plain on other side.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Efavirenz, Lamivudine and Tenofovir disoproxil fumarate is contraindicated in patients with previously demonstrated, clinically significant hypersensitivity (eg, Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the components contained in the formulation.

4.2 Contraindicated Drugs

For some drugs, competition for CYP3A by efavirenz, a component of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate, could result in inhibition of their metabolism and create the potential for serious and/or life-threatening adverse reactions (eg, cardiac arrhythmias, prolonged sedation, or respiratory depression). Drugs that are contraindicated with Efavirenz, Lamivudine and Tenofovir disoproxil fumarate Tablets are listed in Table 1.

Table 1: Drugs That are Contraindicated or Not Recommended for Use with Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets

Drug Class: Drug Name	Clinical Comment
Antimigraine: 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 (NNRTI).

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 lamivudine and tenofovir disoproxil fumarate 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 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 hepatitis B virus (HBV) before initiating antiretroviral therapy. Discontinuation of anti-HBV therapy, including lamivudine and tenofovir disoproxil fumarate, may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue Efavirenz, Lamivudine and Tenofovir disoproxil fumarate should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted.

Important Differences Among Lamivudine-Containing Products: Lamivudine Tablets contain a higher dose of the same active ingredient (lamivudine) than EPIVIR-HBV Tablets. EPIVIR-HBV was developed for patients with chronic hepatitis B. The formulation and dosage of lamivudine in EPIVIR-HBV are not appropriate for patients co-infected with HIV-1 and HBV. Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients co-infected with HIV-1 and HBV.

If treatment with EPIVIR-HBV or tenofovir disoproxil fumarate-containing product such as VIREAD is prescribed for chronic hepatitis B for a patient with unrecognized or untreated HIV-1 infection, rapid emergence of HIV-1 resistance is likely to result because of the subtherapeutic dose and the inappropriateness of monotherapy HIV-1 treatment.

5.3 Coadministration with Other Products

Efavirenz, Lamivudine and Tenofovir disoproxil fumarate is a fixed dose combination product of efavirenz, lamivudine and tenofovir disoproxil fumarate and should not be coadministered comcomitantly with other efavirenz-containing, lamivudine-containing, tenofovir-containing, or emtricitabine-containing drugs, including COMBIVIR® (lamivudine/zidovudine), EPIVIR® or EPIVIR-HBV® (lamivudine), EPZICOM® (abacavir sulfate/lamivudine), TRIZIVIR® (abacavir sulfate/lamivudine/zidovudine), EMTRIVA® (emtricitabine), TRUVADA® (emtricitabine/tenofovir disoproxil fumarate), VIREAD (tenofovir disoproxil fumarate), ATRIPLA® (emtricitabine/efavirenz/tenofovir disoproxil fumarate), COMPLERA® (rilpivirine/ emtricitabine/tenofovir), or STRIBILD® (elvitegravir/cobicistat/tenofovir/emtricitabine).

Efavirenz, Lamivudine and Tenofovir disoproxil fumarate should not be administered in combination with HEPSERA® (adefovir dipivoxil) *[See Drug Interactions (7.6)]*.

5.4 Use With Interferon- and Ribavirin-Based Regimens

In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine, a component of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV-1/HCV co-infected patients *[see Clinical Pharmacology (12.3)]*, hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin. Patients receiving interferon alfa with or without ribavirin and lamivudine should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of lamivudine should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Child-Pugh >6). See the complete prescribing information for interferon and ribavirin.

5.5 Pancreatitis

In pediatric patients with a history of prior antiretroviral nucleoside exposure, a history of pancreatitis, or other significant risk factors for the development of pancreatitis, lamivudine should be used with caution. Treatment with Efavirenz, Lamivudine and Tenofovir disoproxil fumarate should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur.

5.6 New Onset or Worsening Renal Impairment

Tenofovir, a component of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate is principally eliminated by the kidney. 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 disoproxil fumarate *[See Adverse Reactions (6.2)]*.

It is recommended that estimated creatinine clearance be assessed in all patients prior to initiating therapy and as clinically appropriate during therapy with tenofovir disoproxil fumarate. In patients at risk of renal dysfunction, including patients who have previously experienced renal events while receiving HEPSERA® (adefovir dipivoxil), it is recommended that estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein be assessed prior to initiation of tenofovir disoproxil fumarate, and periodically during tenofovir disoproxil fumarate therapy.

Efavirenz, Lamivudine and Tenofovir disoproxil fumarate should be avoided with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs)) *[See Drug Interactions (7.7)]*. Cases of acute renal failure after initiation of high dose or multiple NSAIDs have been reported in HIV-infected patients with risk factors for renal dysfunction who appeared stable on tenofovir DF. Some patients required hospitalization and renal replacement therapy. Alternatives to NSAIDs should be considered, if needed, in patients at risk for renal dysfunction.

Persistent or worsening bone pain, pain in extremities, fractures and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function in at-risk patients.

5.7 Psychiatric Symptoms

Serious psychiatric adverse experiences have been reported in patients treated with efavirenz, a component of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate. In controlled trials of 1008 patients treated with regimens containing efavirenz for a mean of 2.1 years and 635 patients treated with control regimens for a mean of 1.5 years, the frequency (regardless of causality) of specific serious psychiatric events among patients who received efavirenz or control regimens, respectively, were severe depression (2.4%, 0.9%), suicidal ideation (0.7%, 0.3%), nonfatal suicide attempts (0.5%, 0), aggressive behavior (0.4%, 0.5%), paranoid reactions (0.4%, 0.3%), and manic reactions (0.2%, 0.3%). When psychiatric symptoms similar to those noted above were combined and evaluated as a group in a multifactorial analysis of data from Study 006, treatment with efavirenz was associated with an increase in the occurrence of these selected psychiatric symptoms. Other factors associated with an increase in the occurrence of these psychiatric symptoms were history of injection drug use, psychiatric history, and receipt of psychiatric medication at study entry; similar associations were observed in both the efavirenz and control treatment groups. In Study 006, onset of new serious psychiatric symptoms occurred throughout the study for both efavirenz-treated and control-treated patients. One percent of efavirenz-treated patients discontinued or interrupted treatment because of one or more of these selected psychiatric symptoms. There have also been occasional 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.

5.8 Nervous System Symptoms

Fifty-three percent (531/1008) of patients receiving efavirenz, a component of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate, in controlled trials reported central nervous system symptoms (any grade, regardless of causality) compared to 25% (156/635) of patients receiving control regimens. These symptoms included, but were not limited to, dizziness (28.1% of the 1008 patients), insomnia (16.3%), impaired concentration (8.3%), somnolence (7.0%), abnormal dreams (6.2%), and hallucinations (1.2%). These symptoms were severe in 2.0% of patients and 2.1% of patients discontinued therapy as a result. These symptoms usually begin during the first or second day of therapy and generally resolve after the first 2 to 4 weeks of therapy. After 4 weeks of therapy, the prevalence of nervous system symptoms of at least moderate severity ranged from 5% to 9% in patients treated with regimens containing efavirenz and from 3% to 5% in patients treated with a control regimen. Patients should be informed that these common symptoms were likely to improve with continued therapy and were not predictive of subsequent onset of the less frequent psychiatric symptoms [see *Warnings and Precautions (5.7)*]. Dosing at bedtime may improve the tolerability of these nervous system symptoms [see *Dosage and Administration (2.1)*].

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

Patients receiving efavirenz should be alerted to the potential for additive central nervous system effects when efavirenz 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.

5.9 Reproductive Risk Potential

Pregnancy Category D. Efavirenz, a component of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate, may cause fetal harm when administered during the first trimester to a pregnant woman. Pregnancy should be avoided in women receiving efavirenz. Barrier contraception must always be used in combination with other methods of contraception (eg, oral or other hormonal contraceptives). Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of efavirenz is recommended. Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz. 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 in pregnant women. Efavirenz 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. [See *Use in Specific Populations (8.1)*.]

5.10 Rash

In controlled clinical trials, 26% (266/1008) of patients treated with 600 mg efavirenz experienced new-onset skin rash compared with 17% (111/635) of patients treated in control groups. Rash associated with blistering, moist desquamation, or ulceration occurred in 0.9% (9/1008) of patients treated with efavirenz. The incidence of Grade 4 rash (eg, erythema multiforme, Stevens-Johnson syndrome) in patients treated with efavirenz in all studies and expanded access was 0.1%. Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first 2 weeks of initiating therapy with efavirenz (median time to onset of rash in adults was 11 days) and, in most patients continuing therapy with efavirenz, rash resolves within 1 month (median duration, 16 days). The discontinuation rate for rash in clinical trials was 1.7% (17/1008). Efavirenz can be reinitiated in patients interrupting therapy because of rash. Efavirenz 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. For patients who have had a life-threatening cutaneous reaction (eg, Stephens-Johnson syndrome), alternate therapy should be

considered [See *Contraindications (4.1)]*.

Rash was reported in 26 of 57 pediatric patients (46%) treated with efavirenz capsules. One pediatric patient experienced Grade 3 rash (confluent rash with fever), and two patients had Grade 4 rash (erythema multiforme). The median time to onset of rash in pediatric patients was 8 days. Prophylaxis with appropriate antihistamines before initiating therapy with efavirenz in pediatric patients should be considered.

5.11 Hepatotoxicity

Monitoring of liver enzymes before and during treatment is recommended for patients with underlying hepatic disease, including hepatitis B or C infection; patients with marked transaminase elevations; and patients treated with other medications associated with liver toxicity [see *Use in Specific Populations (8.7)*]. A few of the postmarketing reports of hepatic failure occurred in patients with no pre-existing hepatic disease or other identifiable risk factors [see *Adverse Reactions (6.2)*]. Liver enzyme monitoring should also be considered for patients without pre-existing hepatic dysfunction or other risk factors. In patients with persistent elevations of serum transaminases to greater than five times the upper limit of the normal range, the benefit of continued therapy with efavirenz needs to be weighed against the unknown risks of significant liver toxicity.

5.12 Convulsions

Convulsions have been observed in patients receiving efavirenz, generally in the presence of known medical history of seizures [see *Nonclinical Toxicology (13.2)*]. 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 (7.1)*].

5.13 Lipid Elevations

Treatment with efavirenz has resulted in increases in the concentration of total cholesterol and triglycerides. Cholesterol and triglyceride testing should be performed before initiating efavirenz therapy and at periodic intervals during therapy.

5.14 Bone Effects

Bone Mineral Density

In clinical trials in HIV-1 infected adults, tenofovir disoproxil fumarate was associated with slightly greater decreases in bone mineral density (BMD) and increases in biochemical markers of bone metabolism, suggesting increased bone turnover relative to comparators. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in subjects receiving tenofovir disoproxil fumarate *[See Adverse Reactions (6.1)]*.
Clinical trials evaluating tenofovir disoproxil fumarate in pediatric and adolescent subjects were conducted. Under normal circumstances, BMD increases rapidly in pediatric patients. In HIV-1

infected subjects aged 2 years to less than 18 years, bone effects were similar to those observed in adult subjects and suggest increased bone turnover. Total body BMD gain was less in the tenofovir disoproxil fumarate-treated HIV-1 infected pediatric subjects as compared to the control groups. Similar trends were observed in chronic hepatitis B infected adolescent subjects aged 12 years to less than 18 years. In all pediatric trials, skeletal growth (height) appeared to be unaffected. *[See Adverse Reactions (6.1)]*.
The effects of tenofovir disoproxil fumarate-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. Assessment of BMD should be considered for adults and pediatric patients 12 years of age and older who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. 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.

Mineralization Defects:
Cases of osteomalacia associated with proximal renal tubulopathy, manifested as bone pain or pain in extremities and which may contribute to fractures, have been reported in association with the use of tenofovir disoproxil fumarate *[See Adverse Reactions (6.2)]*. Arthralgias and
muscle pain or weakness have also been reported in cases of proximal renal tubulopathy. Hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving products containing tenofovir DF *[See Warnings and Precautions (5.6)]*.

5.15 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy, including efavirenz, lamivudine and tenofovir disoproxil fumarate. 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.

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

5.16 Fat Redistribution

In HIV-infected patients, 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 combination antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

6 ADVERSE REACTIONS

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)]*.
- Hepatic decompensation in patients co-infected with HIV-1 and Hepatitis C *[See Warnings and Precautions (5.4)]*.
- Pancreatitis *[See Warnings and Precautions (5.5)]*.
- New Onset or Worsening Renal Impairment *[See Warnings and Precautions (5.6)]*.
- Psychiatric symptoms *[see Warnings and Precautions (5.7)]*,
- Nervous system symptoms *[see Warnings and Precautions (5.8)]*,
- Rash *[see Warnings and Precautions (5.10)]*.
- Decreases in Bone Mineral Density *[See Warnings and Precautions (5.14)]*.
- Immune Reconstitution Syndrome *[See Warnings and Precautions (5.15)]*.

6.1 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.

Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate

Treatment-Naïve Patients

Study 903 - Treatment-Emergent Adverse Reactions: The most common adverse reactions seen in a double-blind comparative controlled study in which 600 treatment-naïve subjects received tenofovir disoproxil fumarate (N=299) or stavudine (N=301) in combination with lamivudine and efavirenz for 144 weeks (Study 903) were mild to moderate gastrointestinal events and dizziness.

Mild adverse reactions (Grade 1) were common with a similar incidence in both arms, and included dizziness, diarrhea, and nausea. Selected treatment-emergent moderate to severe adverse reactions are summarized in Table 2.

Table 2 Selected Treatment-Emergent Adverse Reactions[a] (Grades 2 to 4) Reported in ≥5% in Any Treatment Group in Study 903 (0 to 144 Weeks)

	Tenofovir disoproxil fumarate + 3TC + EFV	**d4T + 3TC + EFV**
	N=299	**N=301**
Body as a Whole		
Headache	14%	17%
Pain	13%	12%

Fever	8%	7%
Abdominal pain	7%	12%
Back pain	9%	8%
Asthenia	6%	7%
Digestive System		
Diarrhea	11%	13%
Nausea	8%	9%
Dyspepsia	4%	5%
Vomiting	5%	9%
Metabolic Disorders		
Lipodystrophy[b]	1%	8%
Musculoskeletal		
Arthralgia	5%	7%
Myalgia	3%	5%
Nervous System		
Depression	11%	10%
Insomnia	5%	8%
Dizziness	3%	6%
Peripheral neuropathy[c]	1%	5%
Anxiety	6%	6%
Respiratory		
Pneumonia	5%	5%
Skin and Appendages		
Rash event[d]	18%	12%

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

[b] Lipodystrophy represents a variety of investigator-described adverse events not a protocol-defined syndrome.

[c] Peripheral neuropathy includes peripheral neuritis and neuropathy.

[d] Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash.

Laboratory Abnormalities: With the exception of fasting cholesterol and fasting triglyceride elevations that were more common in the stavudine group (40% and 9%) compared with tenofovir disoproxil fumarate (19% and 1%) respectively, laboratory abnormalities observed in this study occurred with similar frequency in the tenofovir disoproxil fumarate and stavudine treatment arms. A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 3.

Table 3 Grade 3/4 Laboratory Abnormalities Reported in ≥1% of Patients Randomized to Efavirenz, Lamivudine and Tenofovir disoproxil fumarate in Study 903 (0 to 144 Weeks)

	Tenofovir disoproxil fumarate + 3TC + EFV	**d4T + 3TC + EFV**
	N=299	**N=301**
Any ≥ Grade 3 Laboratory Abnormality	36%	42%
Fasting Cholesterol (>240 mg/dL)	19%	40%

Creatine Kinase (M: >990 U/L; F: >845 U/L)	12%	12%
Serum Amylase (>175 U/L)	9%	8%
AST (M: >180 U/L; F: >170 U/L)	5%	7%
ALT (M: >215 U/L; F: >170 U/L)	4%	5%
Hematuria (>100 RBC/HPF)	7%	7%
Neutrophils (<750/mm^3)	3%	1%
Fasting Triglycerides (>750 mg/dL)	1%	9%

Changes in Bone Mineral Density:
In HIV-1 infected adult subjects in Study 903, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in subjects receiving tenofovir disoproxil fumarate + lamivudine + efavirenz (-2.2% ± 3.9) compared with subjects receiving stavudine + lamivudine + efavirenz (-1.0% ± 4.6) through 144 weeks. Changes in BMD at the hip were similar between the two treatment groups (-2.8% ± 3.5 in the tenofovir disoproxil fumarate group vs. -2.4% ± 4.5 in the stavudine group). In both groups, the majority of the reduction in BMD occurred in the first 24–48 weeks of the trial and this reduction was sustained through Week 144. Twenty-eight percent of tenofovir disoproxil fumarate -treated subjects vs. 21% of the stavudine-treated 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 disoproxil fumarate group and 6 subjects in the stavudine group. In addition, there were significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C telopeptide, and urinary N telopeptide) and higher serum parathyroid hormone levels and 1,25 Vitamin D levels in the tenofovir disoproxil fumarate group relative to the stavudine group; however, except for bone-specific alkaline phosphatase, these changes resulted in values that remained within the normal range *[See Warnings and Precautions (5.14)]*.

Pediatrics

Efavirenz

Clinical adverse experiences observed in ≥10% of 57 pediatric patients aged 3 to 16 years who received efavirenz capsules, nelfinavir, and one or more NRTIs in Study ACTG 382 were rash (46%), diarrhea/loose stools (39%), fever (21%), cough (16%), dizziness/lightheaded/fainting (16%), ache/pain/discomfort (14%), nausea/vomiting (12%), and headache (11%). The incidence of nervous system symptoms was 18% (10/57). One patient experienced Grade 3 rash, two patients had Grade 4 rash, and five patients (9%) discontinued because of rash [see *Warnings and Precautions (5.10)*].

Tenofovir disoproxil fumarate

Assessment of adverse reactions is based on two randomized trials (Studies 352 and 321) in 184 HIV-1 infected pediatric subjects (2 to less than 18 years of age) who received treatment with tenofovir disoproxil fumarate (N=93) or placebo/active comparator (N=91) in combination with other antiretroviral agents for 48 weeks. The adverse reactions observed in subjects who received

treatment with tenofovir disoproxil fumarate were consistent with those observed in clinical trials in adults.

Changes in Bone Mineral Density:
Clinical trials in HIV-1 infected children and adolescents evaluated BMD changes. In Study 321 (12 to less than 18 years), the mean rate of BMD gain at Week 48 was less in the tenofovir disoproxil fumarate compared to the placebo treatment group. Six tenofovir disoproxil fumarate treated subjects and one placebo treated subject had significant (greater than 4%) lumbar spine BMD loss at Week 48. Changes from baseline BMD Z-scores were -0.341 for lumbar spine and -0.458 for total body in the 28 subjects who were treated with tenofovir disoproxil fumarate for 96 weeks. In Study 352 (2 to less than 12 years), the mean rate of BMD gain in lumbar spine at Week 48 was similar between the tenofovir disoproxil fumarate and the d4T or AZT treatment groups. Total body BMD gain was less in the tenofovir disoproxil fumarate compared to the d4T or AZT treatment groups. One tenofovir disoproxil fumarate-treated subject and none of the d4T or AZT-treated subjects experienced significant (greater than 4%) lumbar spine BMD loss at Week 48. Changes from baseline in BMD Z scores were -0.012 for lumbar spine and -0.338 for total body in the 64 subjects who were treated with tenofovir disoproxil fumarate for 96 weeks. In both trials, skeletal growth (height) appeared to be unaffected *[See Warnings and Precautions (5.14)]*.

6.2 Postmarketing Experience

The following adverse reactions have been reported during postmarketing use for each of the individual components of Efavirenz, Lamivudine, and Tenofovir disoproxil fumarate. Because these reactions are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These reactions have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to lamivudine and tenofovir DF.

Efavirenz

Body as a Whole: allergic reactions, asthenia, redistribution/accumulation of body fat [see *Warnings and Precautions (5.16)*]

Central and Peripheral Nervous System: abnormal coordination, ataxia, cerebellar coordination and balance disturbances, convulsions, hypoesthesia, paresthesia, neuropathy, tremor, vertigo

Endocrine: gynecomastia

Gastrointestinal: constipation, malabsorption

Cardiovascular: flushing, palpitations

Liver and Biliary System: hepatic enzyme increase, hepatic failure, hepatitis. A few of the postmarketing reports of hepatic failure, including cases in patients with no pre-existing hepatic

disease or other identifiable risk factors, were characterized by a fulminant course, progressing in some cases to transplantation or death.

Metabolic and Nutritional: hypercholesterolemia, hypertriglyceridemia

Musculoskeletal: arthralgia, myalgia, myopathy

Psychiatric: aggressive reactions, agitation, delusions, emotional lability, mania, neurosis, paranoia, psychosis, suicide

Respiratory: dyspnea

Skin and Appendages: erythema multiforme, photoallergic dermatitis, Stevens-Johnson syndrome

Special Senses: abnormal vision, tinnitus

Lamivudine

Body as a Whole: Redistribution/accumulation of body fat *[see Warnings and Precautions (5.16)]*.

Endocrine and Metabolic: Hyperglycemia.

General: Weakness.

Hemic and Lymphatic: Anemia (including pure red cell aplasia and severe anemias progressing on therapy).

Hepatic and Pancreatic: Lactic acidosis and hepatic steatosis, posttreatment exacerbation of hepatitis B *[see Boxed Warning, Warnings and Precautions (5.1, 5.2)]*.

Hypersensitivity: Anaphylaxis, urticaria.

Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.

Skin: Alopecia, pruritus.

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

Renal and Urinary Disorders: Renal insufficiency, 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 *[see Warnings and Precautions (5.6)]*.

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

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

No drug interaction studies have been conducted using Efavirenz, Lamivudine and Tenofovir disoproxil fumarate. However, drug interaction studies have been conducted with the individual components efavirenz, lamivudine and tenofovir disoproxil fumarate *[see Clinical Pharmacology (12.3)]*.

Efavirenz

7.1 Drug-Drug Interactions

Efavirenz has been shown *in vivo* to induce CYP3A and CYP2B6. Other compounds that are substrates of CYP3A or CYP2B6 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 (eg, phenobarbital, rifampin, rifabutin) would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations. Drug interactions with efavirenz are summarized in Tables 1 and 4 [for pharmacokinetics data see *Clinical Pharmacology (12.3, Tables 5* and 6*)*]. The tables include potentially significant interactions, but are not all inclusive.

Table 4: Established and Other Potentially Significant 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**
HIV antiviral agents		
Protease inhibitor: Fosamprenavir calcium	↓ amprenavir	Fosamprenavir (unboosted): Appropriate doses of the combinations 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 efavirenz is administered with fosamprenavir/ritonavir once daily. No change in the ritonavir dose is required when efavirenz is administered with fosamprenavir plus ritonavir twice daily.
Protease inhibitor: Atazanavir	↓ atazanavir*	*Treatment-naïve patients:* When coadministered with efavirenz, the recommended dose of atazanavir is 400 mg with ritonavir 100 mg (together once daily with food) and efavirenz 600 mg (once daily on an empty stomach, preferably at bedtime). *Treatment-experienced patients:* Coadministration of efavirenz and atazanavir is not recommended.
Protease inhibitor: Indinavir	↓ indinavir*	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. When indinavir at an increased dose (1000 mg every 8 hours) was given with efavirenz (600 mg once daily), the indinavir AUC and C_{min} were decreased on average by 33 to 46% and 39 to 57%, respectively, compared to when indinavir (800 mg every 8 hours) was given alone.
Protease inhibitor: Lopinavir/ritonavir	↓ lopinavir*	Lopinavir/ritonavir tablets should not be administered once daily in combination with efavirenz. In antiretroviral-naive patients, lopinavir/ritonavir tablets can be used twice daily in combination with efavirenz with no dose adjustment. A dose increase of lopinavir/ritonavir tablets 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). A dose increase of lopinavir/ritonavir oral solution to 533/133 mg (6.5 mL) twice daily taken with food is recommended when used in combination with efavirenz.

Concomitant Drug Class: Drug Name	Effect	Clinical Comment
Protease inhibitor: Ritonavir	↑ ritonavir* ↑ efavirenz*	When ritonavir 500 mg q12h was coadministered with efavirenz 600 mg once daily, the combination was associated with a higher frequency of adverse clinical experiences (eg, dizziness, nausea, paresthesia) and laboratory abnormalities (elevated liver enzymes). Monitoring of liver enzymes is recommended when efavirenz is used in combination with ritonavir.
Protease inhibitor: Saquinavir	↓ saquinavir*	Should not be used as sole protease inhibitor in combination with efavirenz.
NNRTI: Other NNRTIs	↑ or ↓ efavirenz and/or NNRTI	Combining two NNRTIs has not been shown to be beneficial. Efavirenz should not be coadministered with other NNRTIs.
CCR5 co-receptor antagonist: Maraviroc	↓ maraviroc*	Refer to the full prescribing information for maraviroc for guidance on Coadministration with efavirenz.
Integrase strand transfer inhibitor: Raltegravir	↓ raltregravir*	Efavirenz reduces plasma concentrations of raltegravir. The clinical significance of this interaction has not been directly assessed.
Hepatitis C antiviral agents		
Protease inhibitor: boceprevir	↓ boceprevir*	Plasma trough concentrations of boceprevir were decreased when boceprevir was coadministered with efavirenz, which may result in loss of therapeutic effect. The combination should be avoided.
Protease inhibitor: Telaprevir	↓ telaprevir* ↓ efavirenz*	Concomitant administration of telaprevir and efavirenz resulted in reduced steady-state exposures to telaprevir and efavirenz.
Other agents		
Anticoagulant: Warfarin	↑ or ↓ warfarin	Plasma concentrations and effects potentially increased or decreased by efavirenz.
Anticonvulsants: Carbamazepine	↓ carbamazepine* ↓ efavirenz*	There are insufficient data to make a dose recommendation for efavirenz. Alternative anticonvulsant treatment should be used.
Phenytoin Phenobarbital	↓ anticonvulsant ↓ efavirenz	Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.
Antidepressants: Bupropion Sertraline	↓ bupropion* ↓ sertraline*	The effect of efavirenz on bupropion exposure is thought to be due to the induction of bupropion metabolism. Increases in bupropion dosage should be guided by clinical response, but the maximum recommended dose of bupropion should not be exceeded. Increases in sertraline dosage should be guided by clinical response.

Concomitant Drug Class: Drug Name	Effect	Clinical Comment
Antifungals: Voriconazole	↓ voriconazole* ↑ efavirenz*	Efavirenz and voriconazole must not be coadministered at standard doses. 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. When voriconazole is coadministered with efavirenz, voriconazole maintenance dose should be increased to 400 mg every 12 hours and efavirenz dose should be decreased to 300 mg once daily using the capsule formulation. Efavirenz tablets should not be broken. [*Clinical Pharmacology (12.3, Tables 5* and *6)*.]
Itraconazole	↓ itraconazole* ↓ hydroxyitraconazole*	Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered.
Ketoconazole	↓ ketoconazole	Drug interaction studies with efavirenz and ketoconazole have not been conducted. Efavirenz has the potential to decrease plasma concentrations of ketoconazole.
Posaconazole	↓ posaconazole*	Avoid concomitant use unless the benefit outweighs the risks.
Anti-infective: Clarithromycin	↓ clarithromycin* ↑ 14-OH metabolite*	Plasma concentrations decreased by efavirenz; clinical significance unknown. In uninfected volunteers, 46% developed rash while receiving efavirenz and clarithromycin. No dose adjustment of efavirenz is recommended when given with clarithromycin. Alternatives to clarithromycin, such as azithromycin, should be considered (see *Other Drugs*, following table). Other macrolide antibiotics, such as erythromycin, have not been studied in combination with efavirenz.
Antimycobacterial: Rifabutin	↓ rifabutin*	Increase daily dose of rifabutin by 50%. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week.
Rifampin	↓ efavirenz*	If efavirenz is coadministered with rifampin to patients weighing 50 kg or more, an increase in the dose of efavirenz to 800 mg once daily is recommended.

Concomitant Drug Class: Drug Name	Effect	Clinical Comment
Calcium channel blockers: Diltiazem	↓diltiazem* ↓ desacetyl diltiazem* ↓ N-monodesmethyl diltiazem*	Diltiazem dose adjustments should be guided by clinical response (refer to the full prescribing information for diltiazem). No dose adjustment of efavirenz is necessary when administered with diltiazem.
Others (eg, 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 full prescribing information for the calcium channel blocker).
HMG-CoA reductase inhibitors: Atorvastatin Pravastatin Simvastatin	↓ atorvastatin* ↓ pravastatin* ↓ simvastatin*	Plasma concentrations of atorvastatin, pravastatin, and simvastatin decreased. Consult the full prescribing information for the HMG-CoA reductase inhibitor for guidance on individualizing the dose.
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	↓ immunosuppressant	Decreased exposure of the immunosuppressant may be expected due to CYP3A induction. 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 efavirenz.

Concomitant Drug Class: Drug Name	Effect	Clinical Comment
Narcotic analgesic: Methadone	↓ methadone*	Coadministration in HIV-infected individuals with a history of injection drug use resulted in decreased plasma levels of methadone and signs of opiate withdrawal. Methadone dose was increased by a mean of 22% to alleviate withdrawal symptoms. Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.

* The interaction between efavirenz and the drug was evaluated in a clinical study. All other drug interactions shown are predicted.
This table is not all-inclusive.

Other Drugs

Based on the results of drug interaction studies [see *Clinical Pharmacology (12.3, Tables 5* and *6)*], no dosage adjustment is recommended when efavirenz is given with the following: aluminum/magnesium hydroxide antacids, azithromycin, cetirizine, famotidine, fluconazole, lamivudine, lorazepam, nelfinavir, paroxetine, tenofovir disoproxil fumarate, and zidovudine.

Specific drug interaction studies have not been performed with efavirenz and NRTIs other than lamivudine and zidovudine. Clinically significant interactions would not be expected since the NRTIs are metabolized via a different route than efavirenz and would be unlikely to compete for the same metabolic enzymes and elimination pathways.

7.2 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.

Of the three assays analyzed (Microgenics CEDIA DAU Multi-Level THC assay, Cannabinoid Enzyme Immunoassay [Diagnostic Reagents, Inc], and AxSYM Cannabinoid Assay), only the Microgenics CEDIA DAU Multi-Level THC assay showed false-positive
results. The other two assays provided true-negative results. The effects of efavirenz on cannabinoid screening tests other than these three are unknown. The manufacturers of cannabinoid assays should be contacted for additional information regarding the use of their assays with patients receiving efavirenz.

Lamivudine

Lamivudine is predominantly eliminated in the urine by active organic cationic secretion. The possibility of interactions with other drugs administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system (e.g., trimethoprim).

No data are available regarding interactions with other drugs that have renal clearance mechanisms similar to that of lamivudine.

7.3 Interferon- and Ribavirin-Based Regimens

Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV-1/HCV co-infected patients, hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin *[see Warnings and Precautions (5.4), Clinical Pharmacology (12.3)]*.

7.4 Trimethoprim/Sulfamethoxazole (TMP/SMX)

No change in dose of either drug is recommended. There is no information regarding the effect on lamivudine pharmacokinetics of higher doses of TMP/SMX such as those used to treat PCP.

Tenofovir Disoproxil Fumarate

7.5 Didanosine

Coadministration of tenofovir disoproxil fumarate 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.

When administered with tenofovir disoproxil fumarate, the C_{max} and AUC of didanosine (administered as either the buffered or enteric-coated formulation) increased significantly *[See Clinical Pharmacology (12.3)]*. The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis, and neuropathy. Suppression of CD4+ cell counts has been observed in patients receiving tenofovir disoproxil fumarate (tenofovir DF) with didanosine 400 mg daily.

In patients weighing greater than 60 kg, the didanosine dose should be reduced to 250 mg once daily when it is coadministered with tenofovir DF. In patients weighing less than 60 kg, the didanosine dose should be reduced to 200 mg once daily when it is coadministered with tenofovir disoproxil fumarate. When coadministered, tenofovir disoproxil fumarate and didanosine enteric coated capsule may be taken under fasted conditions or with a light meal (less than 400 kcal, 20% fat). For additional information on coadministration of tenofovir disoproxil fumarate and didanosine, please refer to the full prescribing information for didanosine.

7.6 HIV-1 Protease Inhibitors

Tenofovir Disoproxil Fumarate decreases the AUC and C_{min} of atazanavir *[See Clinical Pharmacology (12.3)]*. When coadministered with tenofovir disoproxil fumarate, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. Tenofovir disoproxil fumarate should not be coadministered with atazanavir without ritonavir.

Lopinavir/ritonavir, atazanavir coadministered with ritonavir, and darunavir coadministered with ritonavir have been shown to increase tenofovir concentrations *[See Clinical Pharmacology (12.3)]*. Tenofovir disoproxil fumarate is a substrate of P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP) transporters. When tenofovir disoproxil fumarate is coadministered with an inhibitor of these transporters, an increase in absorption may be observed. Patients receiving tenofovir disoproxil fumarate concomitantly with lopinavir/ritonavir, ritonavir-boosted atazanavir, or ritonavir-boosted darunavirshould be monitored for tenofovir disoproxil fumarate-associated adverse reactions. Tenofovir Disoproxil Fumarate should be discontinued in patients who develop tenofovir disoproxil fumarate-associated adverse reactions.

7.7 Drugs Affecting Renal Function

Since tenofovir is primarily eliminated by the kidneys *[See Clinical Pharmacology (12.3)]*, coadministration of tenofovir disoproxil fumarate with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir and/or increase the concentrations of other renally eliminated drugs. Some examples include, but are not limited to cidofovir, acyclovir, valacyclovir, ganciclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs *[See Warnings and Precautions (5.6)]*.

In the treatment of chronic hepatitis B, tenofovir disoproxil fumarate should not be administered in combination with HEPSERA (adefovir dipivoxil).

8 USE IN SPECIFIC POPULATION

8.1 Pregnancy

Pregnancy Category D: *See Warnings and Precautions (5.9).*

Efavirenz:

As of July 2010, the Antiretroviral Pregnancy Registry has received prospective reports of 792 pregnancies exposed to efavirenz-containing regimens, nearly all of which were first-trimester exposures (718 pregnancies). Birth defects occurred in 17 of 604 live births (first-trimester exposure) and 2 of 69 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 six retrospective reports of findings consistent with neural tube defects, including meningomyelocele. All mothers were exposed to efavirenz-containing regimens in the first trimester. Although a causal relationship of these events to the

use of efavirenz has not been established, similar defects have been observed in preclinical studies of efavirenz.

Animal Data- Effects of efavirenz on embryo-fetal development have been studied in three nonclinical species (cynomolgus monkeys, rats, and rabbits). In monkeys, efavirenz 60 mg/kg/day was administered to pregnant females throughout pregnancy (gestation days 20 through 150). The maternal systemic drug exposures (AUC) were 1.3 times the exposure in humans at the recommended clinical dose (600 mg/day), with fetal umbilical venous drug concentrations approximately 0.7 times the maternal values. Three fetuses of 20 fetuses/infants had one or more malformations; there were no malformed fetuses or infants from placebo-treated mothers. The malformations that occurred in these three monkey fetuses included anencephaly and unilateral anophthalmia in one fetus, microophthalmia in a second, and cleft palate in the third. There was no NOAEL (no observable adverse effect level) established for this study because only one dosage was evaluated. In rats, efavirenz was administered either during organogenesis (gestation days 7 to 18) or from gestation day 7 through lactation day 21 at 50, 100, or 200 mg/kg/day. Administration of 200 mg/kg/day in rats was associated with increase in the incidence of early resorptions; and doses 100 mg/kg/day and greater were associated with early neonatal mortality. The AUC at the NOAEL (50 mg/kg/day) in this rat study was 0.1 times that in humans at the recommended clinical dose. Drug concentrations in the milk on lactation day 10 were approximately 8 times higher than those in maternal plasma. In pregnant rabbits, efavirenz was neither embryo lethal nor teratogenic when administered at doses of 25, 50, and 75 mg/kg/day over the period of organogenesis (gestation days 6 through 18). The AUC at the NOAEL (75 mg/kg/day) in rabbits was 0.4 times that in humans at the recommended clinical dose.

Lamivudine:

Lamivudine pharmacokinetics were studied in pregnant women during 2 clinical studies conducted in South Africa. The study assessed pharmacokinetics in 16 women at 36 weeks gestation using 150 mg lamivudine twice daily with zidovudine, 10 women at 38 weeks gestation using 150 mg lamivudine twice daily with zidovudine, and 10 women at 38 weeks gestation using lamivudine 300 mg twice daily without other antiretrovirals. These studies were not designed or powered to provide efficacy information.

Lamivudine pharmacokinetics in pregnant women were similar to those seen in non-pregnant adults and in postpartum women. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples. In a subset of subjects, lamivudine amniotic fluid specimens were collected following natural rupture of membranes. Amniotic fluid concentrations of lamivudine were typically 2 times greater than maternal serum levels and ranged from 1.2 to 2.5 mcg/mL (150 mg twice daily) and 2.1 to 5.2 mcg/mL (300 mg twice daily). It is not known whether risks of adverse events associated with lamivudine are altered in pregnant women compared with other HIV-1-infected patients.

Animal reproduction studies performed at oral doses up to 130 and 60 times the adult dose in rats and rabbits, respectively, revealed no evidence of teratogenicity due to lamivudine. Increased early embryolethality occurred in rabbits at exposure levels similar to those in humans. However,

there was no indication of this effect in rats at exposure levels up to 35 times those in humans. Based on animal studies, lamivudine crosses the placenta and is transferred to the fetus *[see Nonclinical Toxicology (13.2)]*.

Tenofovir Disoproxil Fumarate:

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, tenofovir disoproxil fumarate should be used during pregnancy only if clearly needed.

Animal Data

Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir.

8.3 Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. Because of both the potential for HIV-1 transmission and serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving Efavirenz, Lamivudine and Tenofovir disoproxil fumarate.

Efavirenz: Although it is not known if efavirenz is secreted in human milk, efavirenz is secreted into the milk of lactating rats.

Lamivudine: Lamivudine is excreted into human milk. Samples of breast milk obtained from 20 mothers receiving lamivudine monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice daily and 300 mg zidovudine twice daily) had measurable concentrations of lamivudine.

Tenofovir Disoproxil Fumarate: Samples of breast milk obtained from five HIV-1 infected mothers in the first post-partum week show that tenofovir is excreted in human milk at low levels. The impact of this exposure in breastfed infants is unknown.

8.4 Pediatric Use

Efavirenz, Lamivudine and Tenofovir disoproxil fumarate Tablets should only be administered to patients greater than 16 years of age with a body weight greater than or equal to 40 kg (greater than or equal to 88 lbs).

8.5 Geriatric Use

Clinical studies of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate 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 patient should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Patients with impaired renal function

Efavirenz, Lamivudine and tenofovir disoproxil fumarate tablets are not recommended for patients with impaired renal function (i.e., creatinine clearance less than 50 mL/min) or patients with end-stage renal disease (ESRD) requiring hemodialysis because they are part of a fixed-dose combination formulation that cannot be adjusted.

8.7 Hepatic Impairment

Efavirenz, a component of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate, is not recommended for patients with moderate or severe hepatic impairment because there are insufficient data to determine whether dose adjustment is necessary. Patients with mild hepatic impairment may be treated with efavirenz without any adjustment in dose. 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 efavirenz to these patients [see *Warnings and Precautions (5.11)* and *Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

If overdose occurs the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.

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

Treatment of overdose with efavirenz should consist of general supportive measures, including monitoring of vital signs and observation of the patient's clinical status. Administration of activated charcoal may be used to aid removal of unabsorbed drug. There is no specific antidote for overdose with efavirenz. Since efavirenz is highly protein bound, dialysis is unlikely to significantly remove the drug from blood.

Lamivudine: There is no known antidote for lamivudine. One case of an adult ingesting 6 grams of lamivudine was reported; there were no clinical signs or symptoms noted and hematologic tests remained normal. Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event.

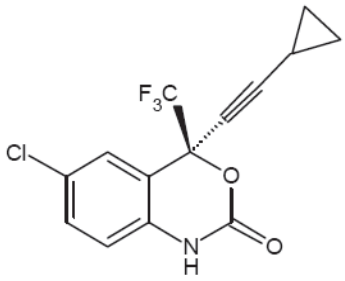
Tenofovir Disoproxil Fumarate: Limited clinical experience at doses higher than the therapeutic dose of tenofovir disoproxil fumarate 300 mg is available. In Study 901, 600 mg tenofovir disoproxil fumarate was administered to 8 subjects orally for 28 days. No severe adverse reactions were reported. The effects of higher doses are not known.

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

11 DESCRIPTION

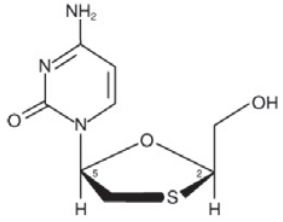
Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets contain a fixed dose combination of efavirenz, lamivudine and tenofovir disoproxil fumarate.

Efavirenz
Efavirenz is an HIV-1 specific, non-nucleoside reverse transcriptase inhibitor (NNRTI). Efavirenz is chemically described as (S)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one. Its empirical 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 microgram/mL).

Lamivudine
Lamivudine is a synthetic nucleoside analogue with activity against HIV-1. The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2′,3′-dideoxy, 3′-thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.3. It has the following structural formula:

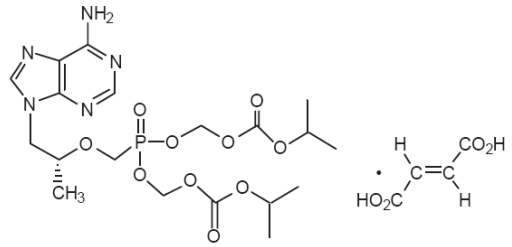


Lamivudine is a white to off-white crystalline solid with a solubility of approximately 70 mg/mL in water at 20°C.

Tenofovir disoproxil fumarate

Tenofovir disoproxil fumarate is a prodrug of tenofovir; it is a fumaric acid salt of bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. *In vivo* tenofovir disoproxil fumarate is converted to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate. Tenofovir exhibits activity against HIV-1 reverse transcriptase.

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 disoproxil fumarate is a white to off-white crystalline powder with a solubility of 13.4 mg/mL in distilled water at 25°C. It has an octanol/phosphate buffer (pH 6.5) partition coefficient (log p) of 1.25 at 25°C.

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are for oral administration. The fixed dose combination tablets contain active ingredients efavirenz 600 mg, lamivudine 300 mg and tenofovir disoproxil fumarate 300 mg.

The inactive ingredients in Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets (600 mg/ 300 mg/ 300 mg) are Croscarmellose Sodium , Hydroxy Propyl Cellulose, Hypromellose, Isopropyl Alcohol, Lactose, Magnesium Stearate, Microcrystalline Cellulose, Opadry II 85G 520033 Yellow, Pregelatinised starch, Sodium Lauryl Sulfate, Yellow oxide of iron.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets are a fixed dose combination of antiviral drugs efavirenz, lamivudine and tenofovir disoproxil fumarate *[see Microbiology (12.4)]*.

12.3 Pharmacokinetics

Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets (600 mg, 300 mg, 300 mg) were bioequivalent to Sustiva® (efavirenz, 600 mg tablet), Epivir® (lamivudine 300 mg tablet) plus Viread® (tenofovir disoproxil fumarate tablet) when administered to healthy volunteers under fasting conditions.

Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets (600 mg, 300 mg, 300 mg) have not been evaluated under fed conditions. Efavirenz and products containing efavirenz should be administered under fasted conditions.

Efavirenz:

In HIV-1 infected subjects time-to-peak plasma concentrations were approximately 3 to 5 hours and steady-state plasma concentrations were reached in 6 to 10 days. In 35 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 to 99.75%) to human plasma proteins, predominantly albumin. Following administration of ^{14}C-labeled efavirenz, 14 to 34% of the dose was recovered in the urine (mostly as metabolites) and 16 to 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 to 76 hours after single doses and 40 to 55 hours after multiple doses.

Lamivudine:

After oral administration of 2 mg/kg of lamivudine twice a day to 9 adults with HIV-1, the peak serum lamivudine concentration (C_{max}) was 1.5 ± 0.5 mcg/mL (mean ± SD). The area under the plasma concentration versus time curve (AUC) and C_{max} increased in proportion to oral dose over the range from 0.25 to 10 mg/kg and absolute bioavailability in 12 adult patients was 86% ± 16% (mean ± SD) for the 150-mg tablet and 87% ± 13% for the oral solution. Binding of lamivudine to human plasma proteins is low (<36%). Within 12 hours after a single oral dose of lamivudine in 6 HIV-l-infected adults, 5.2% ± 1.4% (mean ± SD) of the dose was excreted as the trans-sulfoxide metabolite in the urine. The majority of lamivudine is eliminated unchanged in urine by active organic cationic secretion and the observed mean elimination half-life ($t_{1/2}$) ranged from 5 to 7 hours in most single-dose studies with serum sampling for 24 hours after dosing.

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%. Less than 0.7% of tenofovir binds to human plasma proteins *in vitro* and the binding is independent of concentration over the range of 0.01 to 25 mcg/mL. Approximately 70 to 80% of the intravenous dose of tenofovir is recovered as unchanged drug in the urine. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion 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.

Special Populations

Race

Efavirenz and Lamivudine: There are no significant racial differences in efavirenz and lamivudine pharmacokinetics.

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

Gender:

There are no significant gender differences in the pharmacokinetics of Efavirenz, Lamivudine, and Tenofovir disoproxil fumarate.

Geriatric Patients:

The pharmacokinetics of lamivudine and tenofovir disoproxil fumarate have not been studied in patients over 65 years of age.

Pediatrics:

This combination tablet should not be administered to patients less than or equal to 16 years of age or patients weighing less than 40 kg.

Patients with Impaired Renal Function: *See Use in Specific Populations (8.6)*.

Efavirenz, Lamivudine and Tenofovir disoproxil fumarate is not recommended for patients with impaired renal function (i.e., creatinine clearance less than 50 mL/min) or patients with end-stage renal disease (ESRD) requiring hemodialysis because it is a fixed-dose combination formulation that cannot be adjusted.

Patients with Hepatic Impairment

Efavirenz: A multiple-dose study showed no significant effect on efavirenz pharmacokinetics in patients with mild hepatic impairment (Child-Pugh Class A) compared with controls. There were insufficient data to determine whether moderate or severe hepatic impairment (Child-Pugh Class B or C) affects efavirenz pharmacokinetics.

Lamivudine: The pharmacokinetic properties of lamivudine have been determined in adults with impaired hepatic function. Pharmacokinetic parameters were not altered by diminishing hepatic function; therefore, no dose adjustment for lamivudine is required for patients with impaired hepatic function. Safety and efficacy of lamivudine have not been established in the presence of decompensate liver disease.

Tenofovir disoproxil fumarate: The pharmacokinetics of tenofovir following a 300 mg single dose of tenofovir disoproxil fumarate 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. No change in tenofovir disoproxil fumarate dosing is required in patients with hepatic impairment.

Assessment of Drug Interactions: *See Drug Interactions (7).*

Efavirenz:

Efavirenz has been shown *in vivo* to cause hepatic enzyme induction, thus increasing the biotransformation of some drugs metabolized by CYP3A and CYP2B6. *In vitro* studies have shown that efavirenz inhibited CYP isozymes 2C9, 2C19, and 3A4 with K_i values (8.5 to 17 μM) in the range of observed efavirenz plasma concentrations. In *in vitro* studies, efavirenz did not inhibit CYP2E1 and inhibited CYP2D6 and CYP1A2 (K_i values 82 to 160 μM) only at concentrations well above those achieved clinically. The inhibitory effect on CYP3A is expected to be similar between 200-mg, 400-mg, and 600-mg doses of efavirenz. Coadministration of efavirenz with drugs primarily metabolized by 2C9, 2C19, and 3A 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. The effects of coadministration of efavirenz on the C_{max}, AUC, and C_{min} are summarized in Table 5 (effect of efavirenz on other drugs) and Table 6 (effect of other drugs on efavirenz). For information regarding clinical recommendations see *Contraindications (4.2)* and *Drug Interactions (7.1).*

Table 5: Effect of Efavirenz on Coadministered Drug Plasma C_{max}, AUC, and C_{min}

				Coadministered Drug (mean % change)		
Coadministered Drug	**Dose**	**Efavirenz Dose**	**Number of Subjects**	**C_{max} (90% CI)**	**AUC (90% CI)**	**C_{min} (90% CI)**
Atazanavir	400 mg qd with a light meal d 1-20	600 mg qd with a light meal d 7-20	27	↓ 59% (49-67%)	↓ 74% (68-78%)	↓ 93% (90-95%)
	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%[a] (↓ 17-↑ 58%)	↑ 39%[a] (2-88%)	↑ 48%[a] (24-76%)
	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% (8-27%)	↔	↓ 42% (31-51%)
Indinavir	1000 mg q8h x	600 mg qd x	20			

Table 5: Effect of Efavirenz on Coadministered Drug Plasma C_{max}, AUC, and C_{min}

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Coadministered Drug (mean % change) C_{max} (90% CI)	AUC (90% CI)	C_{min} (90% CI)
	10 days	10 days				
	After morning dose			↔[b]	↓ 33%[b] (26-39%)	↓ 39%[b] (24-51%)
	After afternoon dose			↔[b]	↓ 37%[b] (26-46%)	↓ 52%[b] (47-57%)
	After evening dose			↓ 29%[b] (11-43%)	↓ 46%[b] (37-54%)	↓ 57%[b] (50-63%)
Lopinavir/ ritonavir	400/100 mg capsule q12h x 9 days	600 mg qd x 9 days	11,7[c]	↔[d]	↓ 19%[d] (↓ 36-↑ 3%)	↓ 39%[d] (3-62%)
	600/150 mg tablet q12h x 10 days with efavirenz compared to 400/100 mg q12h alone	600 mg qd x 9 days	23	↑ 36%[d] (28-44%)	↑ 36%[d] (28-44%)	↑ 32%[d] (21-44%)
Nelfinavir	750 mg q8h x 7 days	600 mg qd x 7 days	10	↑ 21% (10-33%)	↑ 20% (8-34%)	↔
Metabolite AG-1402				↓ 40% (30-48%)	↓ 37% (25-48%)	↓ 43% (21-59%)
Ritonavir	500 mg q12h x 8 days	600 mg qd x 10 days	11			
	After AM dose			↑ 24% (12-38%)	↑ 18% (6-33%)	↑ 42% (9-86%)[e]
	After PM dose			↔	↔	↑ 24% (3-50%)[e]
Saquinavir SGC[f]	1200 mg q8h x 10 days	600 mg qd x 10 days	12	↓ 50% (28-66%)	↓ 62% (45-74%)	↓ 56% (16-77%)[e]
Lamivudine	150 mg q12h x 14 days	600 mg qd x 14 days	9	↔	↔	↑ 265% (37-873%)
Tenofovir[g]	300 mg qd	600 mg qd x 14 days	29	↔	↔	↔
Zidovudine	300 mg q12h x 14 days	600 mg qd x 14 days	9	↔	↔	↑ 225% (43-640%)
Maraviroc	100 mg bid	600 mg qd	12	↓ 51% (37-62%)	↓ 45% (38-51%)	↓ 45% (28-57%)
Raltegravir	400 mg single dose	600 mg qd	9	↓ 36% (2-59%)	↓ 36% (20-48%)	↓ 21% (↓ 51-↑ 28%)

Table 5: Effect of Efavirenz on Coadministered Drug Plasma C_{max}, AUC, and C_{min}

			Number of Subjects	Coadministered Drug (mean % change)		
Coadministered Drug	**Dose**	**Efavirenz Dose**		**C_{max} (90% CI)**	**AUC (90% CI)**	**C_{min} (90% CI)**
Boceprevir	800 mg tid x 6 days	600 mg qd x 16 days	NA	↓ 8% (↓ 22-↑ 8%)	↓ 19% (11-25%)	↓ 44% (26-58%)
Telaprevir	750 mg q8h x 10 days	600 mg qd x 20 days	21	↓ 9% (↓ 18-↑ 2%)	↓ 26% (16-35%)	↓ 47% (35-56%)
Azithromycin	600 mg single dose	400 mg qd x 7 days	14	↑ 22% (4-42%)	↔	NA
Clarithromycin	500 mg q12h x 7 days	400 mg qd x 7 days	11	↓ 26% (15-35%)	↓ 39% (30-46%)	↓ 53% (42-63%)
14-OH metabolite				↑ 49% (32-69%)	↑ 34% (18-53%)	↑ 26% (9-45%)
Fluconazole	200 mg x 7 days	400 mg qd x 7 days	10	↔	↔	↔
Itraconazole	200 mg q12h x 28 days	600 mg qd x 14 days	18	↓ 37% (20-51%)	↓ 39% (21-53%)	↓ 44% (27-58%)
Hydroxy-itraconazole				↓ 35% (12-52%)	↓ 37% (14-55%)	↓ 43% (18-60%)
Posaconazole	400 mg (oral suspension) bid x 10 and 20 days	400 mg qd x 10 and 20 days	11	↓ 45% (34-53%)	↓ 50% (40-57%)	NA
Rifabutin	300 mg qd x 14 days	600 mg qd x 14 days	9	↓ 32% (15-46%)	↓ 38% (28-47%)	↓ 45% (31-56%)
Voriconazole	400 mg po q12h x 1 day, then 200 mg po q12h x 8 days	400 mg qd x 9 days	NA	↓ 61%[h]	↓ 77%[h]	NA
	300 mg po q12h days 2-7	300 mg qd x 7 days	NA	↓ 36%[i] (21-49%)	↓ 55%[i] (45-62%)	NA
	400 mg po q12h days 2-7	300 mg qd x 7 days	NA	↑ 23%[i] (↓ 1-↑ 53%)	↓ 7%[i] (↓ 23-↑ 13%)	NA
Atorvastatin	10 mg qd x 4 days	600 mg qd x 15 days	14	↓ 14% (1-26%)	↓ 43% (34-50%)	↓ 69% (49-81%)
Total active (including metabolites)				↓ 15% (2-26%)	↓ 32% (21-41%)	↓ 48% (23-64%)
Pravastatin	40 mg qd x 4 days	600 mg qd x 15 days	13	↓ 32% (↓ 59-↑ 12%)	↓ 44% (26-57%)	↓ 19% (0-35%)
Simvastatin	40 mg qd x 4 days	600 mg qd x 15 days	14	↓ 72%	↓ 68%	↓ 45%

Table 5: Effect of Efavirenz on Coadministered Drug Plasma C_{max}, AUC, and C_{min}

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Coadministered Drug (mean % change)		
				C_{max} (90% CI)	AUC (90% CI)	C_{min} (90% CI)
				(63-79%)	(62-73%)	(20-62%)
Total active (including metabolites)				↓ 68% (55-78%)	↓ 60% (52-68%)	NA[j]
Carbamazepine	200 mg qd x 3 days, 200 mg bid x 3 days, then 400 mg qd x 29 days	600 mg qd x 14 days	12	↓ 20% (15-24%)	↓ 27% (20-33%)	↓ 35% (24-44%)
Epoxide metabolite				↔	↔	↓ 13% (↓ 30-↑ 7%)
Cetirizine	10 mg single dose	600 mg qd x 10 days	11	↓ 24% (18-30%)	↔	NA
Diltiazem	240 mg x 21 days	600 mg qd x 14 days	13	↓ 60% (50-68%)	↓ 69% (55-79%)	↓ 63% (44-75%)
Desacetyl diltiazem				↓ 64% (57-69%)	↓ 75% (59-84%)	↓ 62% (44-75%)
N-monodes-methyl diltiazem				↓ 28% (7-44%)	↓ 37% (17-52%)	↓ 37% (17-52%)
Ethinyl estradiol/ Norgestimate	0.035 mg/0.25 mg x 14 days	600 mg qd x 14 days				
Ethinyl estradiol			21	↔	↔	↔
Norelgestromine			21	↓ 46% (39-52%)	↓ 64% (62-67%)	↓ 82% (79-85%)
Levonorgestrel			6	↓ 80% (77-83%)	↓ 83% (79-87%)	↓ 86% (80-90%)
Lorazepam	2 mg single dose	600 mg qd x 10 days	12	↑ 16% (2-32%)	↔	NA
Methadone	Stable maintenance 35-100 mg daily	600 mg qd x 14-21 days	11	↓ 45% (25-59%)	↓ 52% (33-66%)	NA
Bupropion	150 mg single dose (sustained-release)	600 mg qd x 14 days	13	↓ 34% (21-47%)	↓ 55% (48-62%)	NA
Hydroxy-bupropion				↑ 50% (20-80%)	↔	NA
Paroxetine	20 mg qd x 14 days	600 mg qd x 14 days	16	↔	↔	↔
Sertraline	50 mg qd x 14 days	600 mg qd x 14 days	13	↓ 29%	↓ 39%	↓ 46%

Table 5: Effect of Efavirenz on Coadministered Drug Plasma C_{max}, AUC, and C_{min}

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Coadministered Drug (mean % change) C_{max} (90% CI)	AUC (90% CI)	C_{min} (90% CI)
				(15-40%)	(27-50%)	(31-58%)

↑ Indicates increase ↓ Indicates decrease ↔ Indicates no change or a mean increase or decrease of <10%.

[a] Compared with atazanavir 400 mg qd alone.

[b] Comparator dose of indinavir was 800 mg q8h x 10 days.

[c] Parallel-group design; n for efavirenz + lopinavir/ritonavir, n for lopinavir/ritonavir alone.

[d] Values are for lopinavir; the pharmacokinetics of ritonavir in this study were unaffected by concurrent efavirenz.

[e] 95% CI.

[f] Soft Gelatin Capsule.

[g] Tenofovir disoproxil fumarate.

[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.

NA = not available.

Table 6: Effect of Coadministered Drug on Efavirenz Plasma C_{max}, AUC, and C_{min}

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Efavirenz (mean % change) C_{max} (90% CI)	AUC (90% CI)	C_{min} (90% CI)
Indinavir	800 mg q8h x 14 days	200 mg qd x 14 days	11	↔	↔	↔
Lopinavir/ritonavir	400/100 mg q12h x 9 days	600 mg qd x 9 days	11,12[a]	↔	↓ 16% (↓ 38-↑ 15%)	↓ 16% (↓ 42-↑ 20%)
Nelfinavir	750 mg q8h x 7 days	600 mg qd x 7 days	10	↓ 12% (↓ 32-↑ 13%)[b]	↓ 12% (↓ 35-↑ 18%)[b]	↓ 21% (↓ 53-↑ 33%)
Ritonavir	500 mg q12h x 8 days	600 mg qd x 10 days	9	↑ 14% (4-26%)	↑ 21% (10-34%)	↑ 25% (7-46%)[b]
Saquinavir SGC[c]	1200 mg q8h x 10 days	600 mg qd x 10 days	13	↓ 13% (5-20%)	↓ 12% (4-19%)	↓ 14% (2-24%)[b]
Tenofovir[d]	300 mg qd	600 mg qd x 14 days	30	↔	↔	↔
Boceprevir	800 mg tid x 6 days	600 mg qd x 16 days	NA	↑ 11% (2-20%)	↑ 20% (15-26%)	NA
Telaprevir	750 mg q8h x 10 days	600 mg qd x 20 days	21	↓ 16% (7-24%)	↓ 7% (2-13%)	↓ 2% (↓ 6-↑ 2%)
Telaprevir, coadministered with tenofovir disoproxil fumarate (TDF)	1125 mg q8h x 7 days	600 mg efavirenz /300 mg TDF qd x 7 days	15	↓ 24% (15-32%)	↓ 18% (10-26%)	↓ 10% (↓ 19-↑ 1%)

Table 6: Effect of Coadministered Drug on Efavirenz Plasma C_{max}, AUC, and C_{min}

			Number of Subjects	Efavirenz (mean % change)		
Coadministered Drug	**Dose**	**Efavirenz Dose**		**C_{max} (90% CI)**	**AUC (90% CI)**	**C_{min} (90% CI)**
	1500 mg q12h x 7 days	600 mg efavirenz /300 mg TDF qd x 7 days	16	↓ 20% (14-26%)	↓ 15% (9-21%)	↓ 11% (4-18%)
Azithromycin	600 mg single dose	400 mg qd x 7 days	14	↔	↔	↔
Clarithromycin	500 mg q12h x 7 days	400 mg qd x 7 days	12	↑ 11% (3-19%)	↔	↔
Fluconazole	200 mg x 7 days	400 mg qd x 7 days	10	↔	↑ 16% (6-26%)	↑ 22% (5-41%)
Itraconazole	200 mg q12h x 14 days	600 mg qd x 28 days	16	↔	↔	↔
Rifabutin	300 mg qd x 14 days	600 mg qd x 14 days	11	↔	↔	↓ 12% (↓ 24-↑ 1%)
Rifampin	600 mg x 7 days	600 mg qd x 7 days	12	↓ 20% (11-28%)	↓ 26% (15-36%)	↓ 32% (15-46%)
Voriconazole	400 mg po q12h x 1 day, then 200 mg po q12h x 8 days	400 mg qd x 9 days	NA	↑ 38%[e]	↑ 44%[e]	NA
	300 mg po q12h days 2 - 7	300 mg qd x 7 days	NA	↓ 14%[f] (7-21%)	↔[f]	NA
	400 mg po q12h days 2 - 7	300 mg qd x 7 days	NA	↔[f]	↑ 17%[f] (6-29%)	NA
Atorvastatin	10 mg qd x 4 days	600 mg qd x 15 days	14	↔	↔	↔
Pravastatin	40 mg qd x 4 days	600 mg qd x 15 days	11	↔	↔	↔
Simvastatin	40 mg qd x 4 days	600 mg qd x 15 days	14	↓ 12% (↓ 28-↑ 8%)	↔	↓ 12% (↓ 25-↑ 3%)
Aluminum hydroxide 400 mg, magnesium hydroxide 400 mg, plus simethicone 40 mg	30 mL single dose	400 mg single dose	17	↔	↔	NA
Carbamazepine	200 mg qd x 3 days, 200 mg bid x 3 days, then 400 mg qd x 15 days	600 mg qd x 35 days	14	↓ 21% (15-26%)	↓ 36% (32-40%)	↓ 47% (41-53%)
Cetirizine	10 mg single dose	600 mg qd x 10 days	11	↔	↔	↔

Table 6: Effect of Coadministered Drug on Efavirenz Plasma C_{max}, AUC, and C_{min}

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Efavirenz (mean % change) C_{max} (90% CI)	Efavirenz (mean % change) AUC (90% CI)	Efavirenz (mean % change) C_{min} (90% CI)
Diltiazem	240 mg x 14 days	600 mg qd x 28 days	12	↑ 16% (6-26%)	↑ 11% (5-18%)	↑ 13% (1-26%)
Famotidine	40 mg single dose	400 mg single dose	17	↔	↔	NA
Paroxetine	20 mg qd x 14 days	600 mg qd x 14 days	12	↔	↔	↔
Sertraline	50 mg qd x 14 days	600 mg qd x 14 days	13	↑ 11% (6-16%)	↔	↔

↑ Indicates increase ↓ Indicates decrease ↔ Indicates no change or a mean increase or decrease of <10%.
[a] Parallel-group design; n for efavirenz + lopinavir/ritonavir, n for efavirenz alone.
[b] 95% CI.
[c] Soft Gelatin Capsule.
[d] Tenofovir disoproxil fumarate.
[e] 90% CI not available.
[f] Relative to steady-state administration of efavirenz (600 mg once daily for 9 days).
NA = not available.

Lamivudine:

There was no significant pharmacokinetic interaction between lamivudine and interferon alfa in a study of 19 healthy male subjects *[see Warnings and Precautions (5.4)]*.

In vitro data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV-1/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n = 18), stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug regimen to HIV-1/HCV co-infected patients *[see Warnings and Precautions (5.4)]*.

Lamivudine and TMP/SMX were coadministered to 14 HIV-1-positive patients in a single-center, open-label, randomized, crossover study. Each patient received treatment with a single 300 mg dose of lamivudine and TMP 160 mg/SMX 800 mg once a day for 5 days with concomitant administration of lamivudine 300 mg with the fifth dose in a crossover design.

Coadministration of TMP/SMX with lamivudine resulted in an increase of 43% ± 23% (mean ± SD) in lamivudine AUC_{∞}, a decrease of 29% ± 13% in lamivudine oral clearance, and a decrease of 30% ± 36% in lamivudine renal clearance. The pharmacokinetic properties of TMP and SMX were not altered by coadministration with lamivudine *[see Drug Interactions (7.2)]*.

No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-l-infected adult patients given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg q 12 hr).

Tenofovir Disoproxil Fumarate:

At concentrations substantially higher (~300-fold) than those observed *in vivo*, tenofovir did not inhibit *in vitro* drug metabolism mediated by any of the following human CYP isoforms: CYP3A4, CYP2D6, CYP2C9, or CYP2E1. However, a small (6%) but statistically significant reduction in metabolism of CYP1A substrate was observed. Based on the results of *in vitro* experiments and the known elimination pathway of tenofovir, the potential for CYP mediated interactions involving tenofovir disoproxil fumarate with other medicinal products is low.

Tenofovir Disoproxil Fumarate has been evaluated in healthy volunteers in combination with other antiretroviral and potential concomitant drugs. Tables 7 and 8 summarize pharmacokinetic effects of coadministered drug on tenofovir pharmacokinetics and effects of tenofovir disoproxil fumarate on the pharmacokinetics of coadministered drug. Coadministration of tenofovir disoproxil fumarate with didanosine results in changes in the pharmacokinetics of didanosine that may be of clinical significance. Concomitant dosing of tenofovir disoproxil fumarate with didanosine significantly increases the Cmax and AUC of didanosine. When didanosine 250 mg enteric-coated capsules were administered with tenofovir disoproxil fumarate, systemic exposures of didanosine were similar to those seen with the 400 mg entericcoated capsules alone under fasted conditions (Table 8). The mechanism of this interaction is unknown.

No clinically significant drug interactions have been observed between tenofovir and efavirenz, methadone, nelfinavir, oral contraceptives, or ribavirin.

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

Coadministered Drug	**Dose of Coadministered Drug (mg)**	**N**	**% Change of Tenofovir Pharmacokinetic Parameters[b] (90% CI)**		
			C_{max}	**AUC**	**C_{min}**
Abacavir	300 once	8	⇔	⇔	NC
Atazanavir[c]	400 once daily × 14 days	33	↑ 14 (↑ 8 to ↑ 20)	↑ 24 (↑ 21 to ↑ 28)	↑ 22 (↑ 15 to ↑ 30)
Atazanavir/ Ritonavir[c]	300/100 once daily	12	↑ 34 (↑ 20 to ↑ 51)	↑ 37 (↑ 30 to ↑ 45)	↑ 29 (↑ 21 to ↑ 36)
Darunavir/Ritonavir[d]	300/100 twice daily	12	↑ 24 (↑ 8 to ↑ 42)	↑ 22 (↑ 10 to ↑ 35)	↑ 37 (↑ 19 to ↑ 57)
Didanosine[e]	250 or 400 once daily × 7 days	14	⇔	⇔	⇔
Emtricitabine	200 once daily × 7 days	17	⇔	⇔	⇔
Entecavir	1 mg once daily x 10 days	28	⇔	⇔	⇔
Indinavir	800 three times daily × 7 days	13	↑ 14 (↓ 3 to ↑ 33)	⇔	⇔

Lamivudine	150 twice daily × 7 days	15	⇔	⇔	⇔
Lopinavir/Ritonavir	400/100 twice daily × 14 days	24	⇔	↑ 32 (↑ 25 to ↑ 38)	↑ 51 (↑ 37 to ↑ 66)
Saquinavir/Ritonavir	1000/100 twice daily × 14 days	35	⇔	⇔	↑ 23 (↑ 16 to ↑ 30)
Tacrolimus	0.05 mg/kg twice daily x 7 days	21	↑ 13 (↑ 1 to ↑ 27)	⇔	⇔
Tipranavir/ Ritonavir[f]	500/100 twice daily	22	↓ 23 (↓ 32 to ↓ 13)	↓ 2 (↓ 9 to ↑ 5)	↑ 7 (↓ 2 to ↑ 17)
	750/200 twice daily (23 doses)	20	↓ 38 (↓ 46 to ↓ 29)	↑ 2 (↓ 6 to ↑ 10)	↑ 14 (↑ 1 to ↑ 27)

[a] Subjects received tenofovir disoproxil fumarate 300 mg once daily.
[b] Increase = ↑; Decrease = ↓; No Effect = ⇔; NC = Not Calculated
[c] Reyataz (atazanavir) Prescribing Information
[d] darunavir Prescribing Information
[e] Subjects received didanosine buffered tablets.
[f] tipranavir Prescribing Information

Table 8 Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Tenofovir Disoproxil Fumarate

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Coadministered Drug Pharmacokinetic Parameters[a] (90% CI)		
			C_{max}	AUC	C_{min}
Abacavir	300 once	8	↑ 12 (↓ 1 to ↑ 26)	⇔	NA
Atazanavir[b]	400 once daily × 14 days	34	↓ 21 (↓ 27 to ↓ 14)	↓ 25 (↓ 30 to ↓ 19)	↓ 40 (↓ 48 to ↓ 32)
Atazanavir[b]	Atazanavir/Ritonavir 300/100 once daily × 42 days	10	↓ 28 (↓ 50 to ↑ 5)	↓ 25[c] (↓ 42 to ↓ 3)	↓ 23[c] (↓ 46 to ↑ 10)
Darunavir[d]	Darunavir/Ritonavir 300/100 mg once daily	12	↑ 16 (↓ 6 to ↑ 42)	↑ 21 (↓ 5 to ↑ 54)	↑ 24 (↓ 10 to ↑ 69)
Didanosine[e]	250 once, simultaneously with tenofovir and a light meal[f]	33	↓ 20[g] (↓ 32 to ↓ 7)	⇔[g]	NA
Emtricitabine	200 once daily × 7 days	17	⇔	⇔	↑ 20 (↑ 12 to ↑ 29)
Entecavir	1 mg once daily x 10 days	28	⇔	↑ 13 (↑ 11 to ↑ 15)	⇔
Indinavir	800 three times daily × 7 days	12	↓ 11 (↓ 30 to ↑ 12)	⇔	⇔
Lamivudine	150 twice daily × 7 days	15	↓ 24 (↓ 34 to ↓ 12)	⇔	⇔

Lopinavir Ritonavir	Lopinavir/Ritonavir 400/100 twice daily × 14 days	24	⇔ ⇔	⇔ ⇔	⇔ ⇔
Saquinavir Ritonavir	Saquinavir/Ritonavir 1000/100 twice daily × 14 days	32	↑ 22 (↑ 6 to ↑ 41) ⇔	↑ 29[h] (↑ 12 to ↑ 48) ⇔	↑ 47[h] (↑ 23 to ↑ 76) ↑ 23 (↑ 3 to ↑ 46)
Tacrolimus	0.05 mg/kg twice daily x 7 days	21	⇔	⇔	⇔
Tipranavir[i]	Tipranavir/Ritonavir 500/100 twice daily	22	↓ 17 (↓ 26 to ↓ 6)	↓ 18 (↓ 25 to ↓ 9)	↓ 21 (↓ 30 to ↓ 10)
	Tipranavir/Ritonavir 750/200 twice daily (23 doses)	20	↓ 11 (↓ 16 to ↓ 4)	↓ 9 (↓ 15 to ↓ 3)	↓ 12 (↓ 22 to 0)

[a] Increase = ↑; Decrease = ↓; No Effect = ⇔; NA = Not Applicable
[b] Reyataz (atazanavir) Prescribing Information
[c] 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.
[d] darunavir Prescribing Information
[e] Videx EC Prescribing Information. Subjects received didanosine enteric-coated capsules.
[f] 373 kcal, 8.2 g fat
[g] Compared with didanosie (enteric-coated) 400 mg administered alone under fasting conditions.
[h] Increases in AUC and C_{min} are not expected to be clinically relevant; hence no dose adjustments are required when tenofovir DF and ritonavir-boosted saquinavir are coadministered.
[i] tipranavir Prescribing Information

12.4 Microbiology

Mechanism of Action

Efavirenz: Efavirenz is an NNRTI 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.

Lamivudine: Intracellularly, lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is inhibition of reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue. 3TC-TP is a weak inhibitor of cellular DNA polymerases α, β, and γ.

Tenofovir Disoproxil Fumarate: Tenofovir disoproxil fumarate is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir disoproxil fumarate requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate, an obligate chain terminator. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase and HBV polymerase 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: The concentration of efavirenz inhibiting replication of wild-type laboratory adapted strains and clinical isolates in cell culture by 90 to 95% ($EC_{90 \text{ to } 95}$) ranged from 1.7 to 25 nM in lymphoblastoid cell lines, peripheral blood mononuclear cells (PBMCs), and macrophage/monocyte cultures. Efavirenz demonstrated antiviral activity against clade B and most non-clade B isolates (subtypes A, AE, AG, C, D, F, G, J, N), but had reduced antiviral activity against group O viruses. Efavirenz demonstrated additive antiviral activity without cytotoxicity against HIV-1 in cell culture when combined with the NNRTIs delavirdine (DLV) and nevirapine (NVP), NRTIs (abacavir, didanosine, emtricitabine, lamivudine [LAM], stavudine, tenofovir, zalcitabine, zidovudine [ZDV]), PIs (amprenavir, indinavir [IDV], lopinavir, nelfinavir, ritonavir, saquinavir), and the fusion inhibitor enfuvirtide. Efavirenz demonstrated additive to antagonistic antiviral activity in cell culture with atazanavir. Efavirenz was not antagonistic with adefovir, used for the treatment of hepatitis B virus infection, or ribavirin, used in combination with interferon for the treatment of hepatitis C virus infection.

Lamivudine: The antiviral activity of lamivudine tenofovir against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes) using standard susceptibility assays. EC_{50} values (50% effective concentrations) were in the range of 0.003 to 15 μM (1 μM = 0.23 mcg/mL). HIV-1 from therapy-naive subjects with no amino acid substitutions associated with resistance gave median EC_{50} values of 0.429 μM (range: 0.200 to 2.007 μM) from Virco (n = 92 baseline samples from COLA40263) and 2.35 μM (1.37 to 3.68 μM) from Monogram Biosciences (n = 135 baseline samples from ESS30009). The EC_{50} values of lamivudine against different HIV-1 clades (A-G) ranged from 0.001 to 0.120 μM, and against HIV-2 isolates from 0.003 to 0.120 μM in peripheral blood mononuclear cells. Ribavirin (50 μM) decreased the anti-HIV-1 activity of lamivudine by 3.5 fold in MT-4 cells. In HIV–1-infected MT-4 cells, lamivudine in combination with zidovudine at various ratios exhibited synergistic antiretroviral activity. Please see the full prescribing information for EPIVIR-HBV (lamivudine) for information regarding the inhibitory activity of lamivudine against HBV.

Tenofovir Disoproxil Fumarate: The antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The EC_{50} (50% effective concentration) values for tenofovir were in the range of 0.04 μM to 8.5 μM. In drug combination studies, tenofovir was not antagonistic with nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, 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 μM to 2.2 μM) and strain specific activity against HIV-2 (EC_{50} values ranged from 1.6 μM to 5.5 μM).

Resistance

Efavirenz: In cell culture, HIV-1 isolates with reduced susceptibility to efavirenz (>380-fold increase in EC_{90} value) emerged rapidly in the presence of drug. Genotypic characterization of

these viruses identified single amino acid substitutions L100I or V179D, double substitutions L100I/V108I, and triple substitutions L100I/V179D/Y181C in RT.

Clinical isolates with reduced susceptibility in cell culture to efavirenz have been obtained. One or more RT substitutions at amino acid positions 98, 100, 101, 103, 106, 108, 188, 190, 225, and 227 were observed in patients failing treatment with efavirenz in combination with IDV, or with ZDV plus LAM. The mutation K103N was the most frequently observed. Long-term resistance surveillance (average 52 weeks, range 4 to 106 weeks) analyzed 28 matching baseline and virologic failure isolates. Sixty-one percent (17/28) of these failure isolates had decreased efavirenz susceptibility in cell culture with a median 88-fold change in efavirenz susceptibility (EC_{50} value) from reference. The most frequent NNRTI substitution to develop in these patient isolates was K103N (54%). Other NNRTI substitutions that developed included L100I (7%), K101E/Q/R (14%), V108I (11%), G190S/T/A (7%), P225H (18%), and M230I/L (11%).

Lamivudine: Lamivudine-resistant variants of HIV-1 have been selected in cell culture. Genotypic analysis showed that the resistance was due to a specific amino acid substitution in the HIV-1 reverse transcriptase at codon 184 changing the methionine to either isoleucine or valine (M184V/I).

HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from patients. Susceptibility of clinical isolates to lamivudine and zidovudine was monitored in controlled clinical trials. In patients receiving lamivudine monotherapy or combination therapy with lamivudine plus zidovudine, HIV-1 isolates from most patients became phenotypically and genotypically resistant to lamivudine within 12 weeks. In some patients harboring zidovudine-resistant virus at baseline, phenotypic sensitivity to zidovudine was restored by 12 weeks of treatment with lamivudine and zidovudine. Combination therapy with lamivudine plus zidovudine delayed the emergence of mutations conferring resistance to zidovudine.

Lamivudine-resistant HBV isolates develop substitutions (rtM204V/I) in the YMDD motif of the catalytic domain of the viral reverse transcriptase. rtM204V/I substitutions are frequently accompanied by other substitutions (rtV173L, rtL180M) which enhance the level of lamivudine resistance or act as compensatory mutations improving replication efficiency. Other substitutions detected in lamivudine-resistant HBV isolates include: rtL80I and rtA181T. Similar HBV mutants have been reported in HIV-1-infected patients who received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus *[see Warnings and Precautions (5.2)]*.

Tenofovir Disoproxil Fumarate: HIV-1 isolates with reduced susceptibility to tenofovir have been selected in cell culture. These viruses expressed a K65R substitution in reverse transcriptase and showed a 2 to 4 fold reduction in susceptibility to tenofovir.

In Study 903 of treatment-naïve subjects (tenofovir disoproxil fumarate + lamivudine + efavirenz versus stavudine + lamivudine + efavirenz) *[See Clinical Studies (14.1)]*, genotypic analyses of isolates from subjects with virologic failure through Week 144 showed development of efavirenz and lamivudine resistance-associated substitutions to occur most frequently and with no difference between the treatment arms. The K65R substitution occurred in 8/47 (17%) analyzed

patient isolates on the tenofovir disoproxil fumarate arm and in 2/49 (4%) analyzed patient isolates on the stavudine arm. Of the 8 subjects whose virus developed K65R in the tenofovir disoproxil fumarate arm through 144 weeks, 7 of these occurred in the first 48 weeks of treatment and one at Week 96. Other substitutions resulting in resistance to tenofovir disoproxil fumarate were not identified in this study.

Cross-Resistance

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

Lamivudine: Lamivudine-resistant HIV-1 mutants were cross-resistant to didanosine (ddI). In some patients treated with zidovudine plus didanosine, isolates resistant to multiple reverse transcriptase inhibitors, including lamivudine, have emerged.

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 subjects (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. There was no NOAEL in female established for this study because tumor findings occurred at all doses. AUC at the NOAEL (150 mg/kg) in the males was approximately 0.9 times that in humans at the recommended clinical dose. In the rat study, no increases in tumor incidence were observed at doses up to 100 mg/kg/day, for which AUCs were 0.1 (males) or 0.2 (females) times those in humans at the recommended clinical dose.

Efavirenz tested negative in a battery of *in vitro* and *in vivo* genotoxicity assays. 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.

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. The AUCs at the NOAEL values in male (200 mg/kg) and female (100 mg/kg) rats were approximately ≤0.15 times that in humans at the recommended clinical dose

Lamivudine: Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) those observed in humans at the recommended therapeutic dose for HIV-1 infection. Lamivudine was not active in a microbial mutagenicity screen or an *in vitro* cell transformation assay, but showed weak in vitro mutagenic activity in a cytogenetic assay using cultured human lymphocytes and in the mouse lymphoma assay. However, lamivudine showed no evidence of in vivo genotoxic activity in the rat at oral doses of up to 2,000 mg/kg, producing plasma levels of 35 to 45 times those in humans at the recommended dose for HIV-1 infection. In a study of reproductive performance, lamivudine administered to rats at doses up to 4,000 mg/kg/day, producing plasma levels 47 to 70 times those in humans, revealed no evidence of impaired fertility and no effect on the survival, growth, and development to weaning of the offspring.

Tenofovir Disoproxil Fumarate: Long-term oral carcinogenicity studies of tenofovir disoproxil fumarate 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 Disoproxil Fumarate was mutagenic in the *in vitro* mouse lymphoma assay and negative in an *in vitro* bacterial mutagenicity test (Ames test). In an *in vivo* mouse micronucleus assay, tenofovir disoproxil fumarate was negative when administered to male mice.

There were no effects on fertility, mating performance or early embryonic development when tenofovir disoproxil fumarate 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 [see *Warnings and Precautions (5.12)*].

Lamivudine: Reproduction studies have been performed in rats and rabbits at orally administered

doses up to 4,000 mg/kg/day and 1,000 mg/kg/day, respectively, producing plasma levels up to approximately 35 times that for the adult HIV dose. No evidence of teratogenicity due to lamivudine was observed. Evidence of early embryolethality was seen in the rabbit at exposure levels similar to those observed in humans, but there was no indication of this effect in the rat at exposure levels up to 35 times those in humans. Studies in pregnant rats and rabbits showed that lamivudine is transferred to the fetus through the placenta.

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

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

14 CLINICAL STUDIES

14.1 Clinical Efficacy in Patients with HIV-1 Infection

Treatment-Naïve Adult Patients

Study 903

Data through 144 weeks are reported for Study 903, a double-blind, active-controlled multicenter study comparing tenofovir disoproxil fumarate (300 mg once daily) administered in combination with lamivudine and efavirenz versus stavudine (d4T), lamivudine, and efavirenz in 600 antiretroviral-naïve subjects. Subjects had a mean age of 36 years (range 18 to 64), 74% were male, 64% were Caucasian and 20% were Black. The mean baseline $CD4^+$ cell count was 279 cells/mm^3 (range 3 to 956) and median baseline plasma HIV-1 RNA was 77,600 copies/mL (range 417 to 5,130,000). Subjects were stratified by baseline HIV-1 RNA and $CD4^+$ cell count. Forty-three percent of subjects had baseline viral loads >100,000 copies/mL and 39% had $CD4^+$ cell counts <200 cells/mm^3. Treatment outcomes through 48 and 144 weeks are presented in Table 9.

Table 9 Outcomes of Randomized Treatment at Week 48 and 144 (Study 903)

	At Week 48		At Week 144	
Outcomes	**Tenofovir disoproxil fumarate+3TC +EFV (N=299)**	**d4T+3TC +EFV (N=301)**	**Tenofovir disoproxil fumarate+3TC+EFV (N=299)**	**d4T+3TC+EFV (N=301)**
Responder[a]	79%	82%	68%	62%

Virologic failure[b]	6%	4%	10%	8%
Rebound	5%	3%	8%	7%
Never suppressed	0%	1%	0%	0%
Added an antiretroviral agent	1%	1%	2%	1%
Death	<1%	1%	<1%	2%
Discontinued due to adverse event	6%	6%	8%	13%
Discontinued for other reasons[c]	8%	7%	14%	15%

a. Subjects achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Week 48 and 144.
b. Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Week 48 and 144.
c. Includes lost to follow-up, subject's withdrawal, noncompliance, protocol violation and other reasons.

Achievement of plasma HIV-1 RNA concentrations of less than 400 copies/mL at Week 144 was similar between the two treatment groups for the population stratified at baseline on the basis of HIV-1 RNA concentration (> or ≤100,000 copies/mL) and $CD4^+$ cell count (< or ≥200 cells/mm^3). Through 144 weeks of therapy, 62% and 58% of subjects in the tenofovir disoproxil fumarate and stavudine arms, respectively achieved and maintained confirmed HIV-1 RNA <50 copies/mL. The mean increase from baseline in $CD4^+$ cell count was 263 cells/mm^3 for the tenofovir disoproxil fumarate arm and 283 cells/mm^3 for the stavudine arm. Through 144 weeks, 11 subjects in the tenofovir disoproxil fumarate group and 9 subjects in the stavudine group experienced a new CDC Class C event.

16 HOW SUPPLIED/STORAGE AND HANDLING

Efavirenz, Lamivudine, and Tenofovir disoproxil fumarate Tablets containing 600mg of Efavirenz, 300mg of Lamivudine and 300mg tenofovir disoproxil fumarate are yellow coloured, capsule shaped, biconvex, film coated tablets with "T" debossed on one side & plain on other side. They are available as follows:

Container of 30 tablets each with non child resistant closure NDC 53104-111-01

Storage

Store at room temperature below 30°C (86°F).

17 PATIENT COUNSELING INFORMATION

See *FDA-approved patient labeling (Patient Information)*.

17.1 Information for Patients

Patients should be advised that Efavirenz, Lamivudine and Tenofovir disoproxil fumarate:

- 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.
- is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should remain under the

care of a physician when using Efavirenz, Lamivudine and Tenofovir disoproxil fumarate.

- Patients shoud avoid doing things that can spread HIV-1 infection to others.
  - **Do not share needles or other injection equipment.**
  - **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
  - **Do not have any kind of sex without protection. Always practice safe sex by** using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.
  - **Do not breastfeed.** Lamivudine and tenofovir are excreted in breast milk. Mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

Also:

- The long term effects of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate are unknown.
- Efavirenz, Lamivudine and Tenofovir disoproxil fumarate is for oral ingestion only.
- Efavirenz, Lamivudine and Tenofovir disoproxil fumarate should not be discontinued without first informing their physician.
- It is important to take Efavirenz, Lamivudine and Tenofovir disoproxil fumarate on a regular dosing schedule and to avoid missing doses.
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Treatment with Efavirenz, Lamivudine and Tenofovir disoproxil fumarate should be suspended in any patient who develops 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)]*.
- Patients with HIV-1 should be tested for Hepatitis B virus (HBV) before initiating antiretroviral therapy.
- Severe acute exacerbations of hepatitis have been reported in patients who are infected with HBV or coinfected with HBV and HIV-1 and have discontinued lamivudine and tenofovir disoproxil fumarate tablets, components of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate *[See Warnings and Precautions (5.2)]*.
- Patients with HIV-1/HCV co-infection should be informed that hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin *[see Warnings and Precautions (5.4)]*.
- In patients with chronic hepatitis B, it is important to obtain HIV antibody testing prior to initiating lamivudine and tenofovir disoproxil fumarate tablets, components of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate.
- Renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported. Efavirenz, Lamivudine and Tenofovir disoproxil fumarate should be avoided with concurrent or recent use of a nephrotoxic agent (e.g. high-dose or multiple NSAIDs) and is not recommended for patients with impaired renal function (i.e., creatinine clearance less than 50 mL/min) or patients with end-stage renal disease (ESRD) requiring hemodialysis *[See Dosage and Administration (2.2)]*.
- 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, a component of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate [see *Warnings and Precautions (5.8)*]. 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 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.

- 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 [see *Warnings and Precautions (5.7)*]. If they experience severe psychiatric *adverse experiences they shoul*d seek immediate medical evaluation. Patients should be advised to inform their physician of any history of mental illness or substance abuse.
- Patients should be informed that a common side effect of efavirenz is rash [see *Warnings and Precautions (5.10)*]. 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.
- Women receiving Efavirenz, Lamivudine and Tenofovir disoproxil fumarate should be instructed to avoid pregnancy [see *Warnings and Precautions (5.9)*]. A reliable form of barrier contraception shoul*d always be used in combinatio*n 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 use is recommended. Women should be advised to notify their physician if they become pregnant or plan to become pregnant while taking Efavirenz, Lamivudine and Tenofovir disoproxil fumarate. 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.
- Efavirenz, Lamivudine and Tenofovir disoproxil fumarate should not be administered in combination with HEPSERA (adefovir dipivoxil) *[See Warnings and Precautions (5.3)]*.
- Efavirenz, Lamivudine and Tenofovir disoproxil fumarate should not be coadministered with other efavirenz-containing, lamivudine-containing, tenofovir disoproxil fumarate-containing, or emtricitabine-containing drugs, including COMBIVIR (lamivudine/zidovudine), EPIVIR or EPIVIR-HBV (lamivudine), EPZICOM (abacavir sulfate/lamivudine), or TRIZIVIR (abacavir sulfate/lamivudine/zidovudine), EMTRIVA® (emtricitabine), STRIBILD® (elvitegravir/cobicistat/tenofovir/emtricitabine), ATRIPLA (emtricitabine/efavirenz/tenofovir disoproxil fumarate), or TRUVADA® (emtricitabine/tenofovir disoproxil fumarate) *[See Warnings and Precautions (5.3)]*
- Decreases in bone mineral density have been observed with the use of lamivudine and tenofovir disoproxil fumarate, components of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate, in patients with HIV. Bone mineral density monitoring should be considered in patients who have a history of pathologic bone fracture or at risk for osteopenia *[See Warnings and Precautions (5.14)]*.
- Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy, including Efavirenz, Lamivudine and Tenofovir disoproxil fumarate, and that the cause and long-term health effects of these conditions are not known at this time *[See Warnings and Precautions (5.16)]*.

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Rx only
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Mfd. by CIPLA LTD.
Verna, Goa 403 722 INDIA

Mfd. by CIPLA LTD.
MIDC, Patalganga,
M.S. 410 220 INDIA

PATIENT INFORMATION

Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, 600 mg/300 mg/300 mg

Read this leaflet carefully before you start taking Efavirenz, Lamivudine and Tenofovir disoproxil fumarate and each time you get a refill. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is the most important information I should know about Efavirenz, Lamivudine and Tenofovir disoproxil fumarate?

Efavirenz, Lamivudine and Tenofovir disoproxil fumarate can cause serious side effects, including:

1. **Build-up of an acid in your blood (lactic acidosis).** Lactic acidosis can happen in some people who take Efavirenz, Lamivudine and Tenofovir disoproxil fumarate or similar (nucleoside analog) medicines. **Lactic acidosis** is a serious medical emergency that can lead to death.

   Lactic acidosis can be hard to identify early, because the symptoms could seem like symptoms of other health problems. **Call your healthcare provider right away if you get the following symptoms which could be signs of lactic acidosis:**

   - feeling very weak or tired
   - have unusual (not normal) muscle pain
   - have trouble breathing
   - have stomach pain with
   - nausea (feel sick to your stomach)
   - vomiting
   - feel cold, especially in your arms and legs

- feel dizzy or lightheaded
- have a fast or irregular heartbeat

2. **Severe liver problems.** Severe liver problems can happen in people who take Efavirenz, Lamivudine and Tenofovir disoproxil fumarate or similar medicines. In some cases these liver problems can lead to death. Your liver may become large (hepatomegaly) and you may develop fat in your liver (steatosis).

   Call your healthcare provider right away if you have any of the following symptoms of liver problems:

   - Your skin or the white part of your eyes turns yellow (jaundice).
   - dark "tea-colored" urine
   - light-colored bowl movements (stools)
   - loss of appetite for several days or longer
   - nausea
   - stomach pain

   You may be more likely to get lactic acidosis or severe liver problems if you are female, very overweight (obese), or have been taking Efavirenz, Lamivudine and Tenofovir disoproxil fumarate or a similar medicine for a long time.

3. **Worsening of your Hepatitis B infection.** If you are also infected with hepatitis B Virus (HBV) infection, you need close medical follow-up for several months after stopping treatment with Efavirenz, Lamivudine and Tenofovir disoproxil fumarate. Follow-up includes medical exams and blood test to check for HBV that could be getting worse. A "flare-up" is when your HBV infection suddenly returns in a worse way than before.

4. **Serious psychiatric problems.** A small number of patients experience severe depression, strange thoughts, or angry behavior while taking efavirenz, a component of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate. Some patients have thoughts of suicide and a few have actually committed suicide. These problems tend to occur more often in patients who have had mental illness. Contact your doctor right away if you think you are having these psychiatric symptoms, so your doctor can decide if you should continue to take Efavirenz, Lamivudine and Tenofovir disoproxil fumarate.

What are Efavirenz, Lamivudine and Tenofovir disoproxil fumarate tablets?

Efavirenz, Lamivudine and Tenofovir disoproxil fumarate tablets are a prescription medicine used:

- alone or with other antiviral medicines to treat Human Immunodeficiency Virus (HIV) in adults and pediatric patients weighing at least 40 kg (88 lb). HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome). Efavirenz, Lamivudine and Tenofovir disoproxil fumarate does not cure HIV or AIDS. People taking Efavirenz, Lamivudine and Tenofovir disoproxil fumarate may still get infections common in people with HIV

(opportunistic infections). It is very important that you stay under the care of your healthcare provider.

What should I tell my healthcare provider before taking Efavirenz, Lamivudine and Tenofovir disoproxil fumarate tablets?

Tell your healthcare provider if you:

- have liver problems, including hepatitis B (HBV) infection
- have kidney problems
- have bone problems
- have any other medical conditions, including HIV infection
- are pregnant or plan to become pregnant. You should not become pregnant while taking Efavirenz, Lamivudine and Tenofovir disoproxil fumarate and for 12 weeks after stopping it.
- are breast-feeding or plan to breast-feed. You should not breast-feed if you have HIV infection or AIDS. The virus that causes HIV can pass through your breast milk to your baby. Talk to your healthcare provider about the best way to feed your baby.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements, especially St. John's wort. Efavirenz, Lamivudine and Tenofovir disoproxil fumarate may affect the way other medicines work, and other medicines may affect how Efavirenz, Lamivudine and Tenofovir disoproxil fumarate works.

Do not take Efavirenz, Lamivudine and Tenofovir disoproxil fumarate if you also take:

- other medicines that contain tenofovir (TRUVADA, ATRIPLA, VIREAD, COMPLERA, STRIBILD)
- other medicines that contain lamivudine or emtricitabine (EPIVIR, EPIVIR-HBV, COMBIVIR, EPZICOM, TRIZIVIR, EMTRIVA)
- adefovir (HEPSERA)
- VASCOR (bepridil)
- PROPULSID (cisapride)
- VERSED (midazolam)
- ORAP (pimozide)
- HALCION (triazolam)
- Ergot medications (for example, Wigraine and Cafergot)

The following medicines may need to be replaced with another medicine when taken with Efavirenz, Lamivudine and Tenofovir disoproxil fumarate:

- FORTOVASE, INVIRASE (saquinavir)
- BIAXIN (clarithromycin)
- CARBATROL, TEGRETOL (carbamazepine)
- NOXAFIL (posaconazole)

- SPORANOX (itraconazole)
- REYATAZ (atazanavir sulfate), if this is not the first time you are receiving treatment for your HIV infection
- VICTRELIS (boceprevir)

Especially tell your healthcare provider if you take the following medications, as the dose of these other medications may need to be changed:

- Calcium channel blockers such as Cardizem or Tiazac (diltiazem), Covera HS or Isoptin SR (verapamil), and others.
- The cholesterol-lowering medicines Lipitor (atorvastatin), PRAVACHOL (pravastatin sodium), and Zocor (simvastatin).
- Crixivan (indinavir)
- Kaletra (lopinavir/ritonavir)
- Methadone
- Mycobutin (rifabutin)
- REYATAZ (atazanavir sulfate).
- Rifadin (rifampin) or the rifampin-containing medicines Rifamate and Rifater.
- Selzentry (maraviroc)
- Vfend (voriconazole) and efavirenz, a component of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate must not be taken together at standard doses.
- Zoloft (sertraline)
- Wellbutrin, Wellbutrin SR, Wellbutrin XL, or Zyban (bupropion)
- The immunosuppressant medicines cyclosporine (Gengraf, Neoral, Sandimmune, and others), Prograf (tacrolimus), or Rapamune (sirolimus).
- Didanosine (VIDEX, VIDEX EC)
- Adefovir (HEPSERA)

Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.

How should I take Efavirenz, Lamivudine and Tenofovir disoproxil fumarate?

- See "What is the most important information I should know about Efavirenz, Lamivudine and Tenofovir disoproxil fumarate?"
- Take Efavirenz, Lamivudine and Tenofovir disoproxil fumarate exactly as your healthcare provider tells you to take them.
- Take Efavirenz, Lamivudine and Tenofovir disoproxil fumarate at the same time every day, preferably at bedtime to make some of the side effects less bothersome.
- The usual dose of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate is 1 tablet each day. If you are an adult and have kidney or liver problems, your healthcare provider may tell you not to take Efavirenz, Lamivudine and Tenofovir disoproxil fumarate.
- Take Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets by mouth on an empty stomach.
- Do not miss a dose of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate. If you miss

a dose, take the missed dose as soon as you remember. If it is almost time for your next dose of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate, do not take the missed dose. Take the next dose at your regular time.
- If you take too much Efavirenz, Lamivudine and Tenofovir disoproxil fumarate, call your local poison control center or go right away to the nearest hospital emergency room.

What are the possible side effects of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate?

- **See "What is the most important information I should know about Efavirenz, Lamivudine and Tenofovir disoproxil fumarate"?**
- **New or worse kidney problems** can happen in some people who take Efavirenz, Lamivudine and Tenofovir disoproxil fumarate. If you have had kidney problems in the past or need to take another medicine that can cause kidney problems, your healthcare provider may need to do blood tests to check your kidneys during your treatment with Efavirenz, Lamivudine and Tenofovir disoproxil fumarate.
- **Bone problems** can happen in some people who take Efavirenz, Lamivudine and Tenofovir disoproxil fumarate. Bone problems include bone pain, softening or thinning (which may lead to fractures). Your healthcare provider may need to do additional tests to check your bones.
- **Changes in body fat** can happen in some people who take antiviral medicines. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the main part of your body (trunk). Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known.
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your doctor if you start having new symptoms after starting your HIV medicine.
- **Rash** is common and usually goes away without any change in treatment. In a small number of patients, rash may be serious. If you develop a rash, call your doctor right away. **Rash may be a serious problem in some children.** Tell your child's doctor right away if you notice rash or any other side effects while your child is taking Efavirenz, Lamivudine and Tenofovir disoproxil fumarate.

The most common side effects of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate are:

- nausea
- rash
- diarrhea
- headache
- pain
- depression
- weakness
- fatigue
- nasal signs and symptoms
- cough

- dizziness
- trouble sleeping
- drowsiness

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects.

How do I store Efavirenz, Lamivudine and Tenofovir disoproxil fumarate?

- Store efavirenz, lamivudine and tenofovir disoproxil fumarate tablets below 30ºC.
- Keep efavirenz, lamivudine and tenofovir disoproxil fumarate tablets in the original container.
- Do not use efavirenz, Lamivudine and tenofovir disoproxil fumarate tablets if the seal over the bottle opening is broken or missing.
- Keep the bottle tightly closed.
- **Keep efavirenz, lamivudine and tenofovir disoproxil fumarate tablets and all medicines out of the reach of children**

General information about Efavirenz, Lamivudine and Tenofovir disoproxil fumarate:

Medicines are sometimes prescribed for purposes other than those listed in the patient leaflet. Do not use Efavirenz, Lamivudine and Tenofovir disoproxil fumarate for a condition for which it was not prescribed. Do not give Efavirenz, Lamivudine and Tenofovir disoproxil fumarate to other people, even if they have the same condition you have. It may harm them.

Efavirenz, Lamivudine and Tenofovir disoproxil fumarate does not reduce the risk of passing HIV-1 to others through sexual contact or blood contamination. Continue to practice safer sex and do not use or share dirty needles. Do not share personal items that can have blood or body fluids on them, like toothbrushes or razor blades.

This leaflet summarizes the most important information about lamivudine and tenofovir disoproxil fumarate tablets. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about Efavirenz, Lamivudine and Tenofovir disoproxil fumarate that is written for health professionals.

What are the ingredients in Efavirenz, Lamivudine and Tenofovir disoproxil fumarate?

Active Ingredients: Efavirenz, Lamivudine, Tenofovir disoproxil fumarate

Inactive Ingredients: Croscarmellose Sodium , Hydroxy Propyl Cellulose, Hypromellose, Isopropyl Alcohol, Lactose, Magnesium Stearate, Microcrystalline Cellulose, Opadry II 85G 520033 Yellow, Pregelatinised starch, Sodium Lauryl Sulfate, Yellow oxide of iron.

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M.S. 410 220 INDIA