**WARNINGS: LACTIC ACIDOSIS AND POST TREATMENT EXACERBATIONS 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. (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 type 1 (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)

**ADVERSE REACTIONS**

- 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)
- Convulsions: Use caution in patients with a history of seizures. (5.12)
- Lids: 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)

**DRUG INTERACTIONS**

Co-administration of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets can alter the concentrations of other drugs and other drugs may alter the concentration of efavirenz, lamivudine, and tenofovir disoproxil fumarate. The potential for drug-drug interactions should be considered before and during therapy. (7)

**USING IN SPECIFIC POPULATIONS**

- Pregnancy: Women should avoid pregnancy during efavirenz therapy, a component of Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate tablets, and for 12 weeks after discontinuation. (5.9)
- Lactation: Breastfeeding not recommended. (8.2)
- Females and Males of Reproductive Potential: Pregnancy testing and contraception are recommended. (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. Issued: 11/2017
WARNINGS: LACTIC ACIDOSIS and POST TREATMENT EXACERBATIONS OF HEPATITIS B

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FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS and POST TREATMENT EXACERBATIONS OF HEPATITIS B

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues and other antiretrovirals. Discontinue lamivudine and tenofovir disoproxil fumarate 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. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue lamivudine and tenofovir disoproxil fumarate and are co-infected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted [see Warnings and Precautions (5.2)].

1 INDICATIONS AND USAGE

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are indicated for use alone as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and in pediatric patients weighing at least 40 kg.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for Adult and Pediatric Patients weighing at least 40 kg

The recommended dosage of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets is 600 mg/300 mg/300 mg orally, once daily. It is recommended that efavirenz, lamivudine and tenofovir disoproxil fumarate tablets be taken on an empty stomach, preferably at bedtime. Dosing at bedtime may improve the tolerability of nervous system symptoms [see Warnings and Precautions (5.7), Adverse Reactions (6.1), and Patient Counseling Information (17)]. Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should be swallowed intact with liquid.

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.

2.3 Patient Monitoring

Monitor hepatic function prior to and during treatment with efavirenz, a component of efavirenz, lamivudine, and tenofovir disoproxil fumarate tablets [see Warnings and Precautions (5.11)]. Efavirenz is not recommended in patients with moderate or severe hepatic impairment (Child Pugh B or C) [see Warnings and Precautions (5.11) and Use in Specific Populations (8.7)].
3 DOSAGE FORMS AND STRENGTHS

Efavirenz, Lamivudine and Tenofovir disoproxil fumarate Tablets are white, off-white colored, capsule shaped, biconvex, film coated tablets debossed with “M 9” on one side and plain on the other side containing 600 mg of efavirenz, 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate which is equivalent to 245 mg of tenofovir disoproxil.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

- Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are contraindicated in patients with a previous hypersensitivity reaction to any of the components contained in the formulation.
- Coadministration with elbasvir and grazoprevir is contraindicated [see Drug Interactions (7.5)].

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 and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. 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 Efavirenz, Lamivudine and Tenofovir disoproxil fumarate -HBV Tablets. Efavirenz, Lamivudine and Tenofovir disoproxil fumarate -HBV was developed for patients with chronic hepatitis B. The formulation and dosage of lamivudine in Efavirenz, Lamivudine and Tenofovir disoproxil fumarate -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 lamivudine-HBV or tenofovir disoproxil fumarate-containing product such as Tenofovir disoproxil fumarate 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 tablets are a fixed-dose combination product of efavirenz, lamivudine and tenofovir disoproxil fumarate and should not be coadministered concomitantly 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 tablets should not be administered in combination with HEPESERA® (adefovir dipivoxil) [see Drug Interactions (7.3)].

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 tablets. 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 full 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 tablets 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 tablets 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 tablets 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 (7.3)]. 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 disoproxil fumarate. 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 tablets. 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. Postmarketing cases of catatonia have also been reported and may be associated with increased efavirenz exposure. 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 tablets, 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 Embryo-Fetal Toxicity
Efavirenz, a component of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, may cause fetal harm when administered during the first trimester to a pregnant woman. Advise females of reproductive potential who are receiving efavirenz to avoid pregnancy. [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 reintiated 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
Postmarketing cases of hepatitis, including fulminant hepatitis progressing to liver failure requiring transplantation or resulting in death, have been reported in patients treated with efavirenz. Reports have included patients with underlying hepatic disease, including coinfection with hepatitis B or C, and patients without pre-existing hepatic disease or other identifiable risk factors.

Efavirenz is not recommended for patients with moderate or severe hepatic impairment. Careful monitoring is recommended for patients with mild hepatic impairment receiving efavirenz. [see Adverse Reactions (6.1) and Use in Specific Populations (8.6)]. Monitoring of liver enzymes before and during treatment is recommended for all patients [see Dosage and Administration (2.1)]. Consider discontinuing efavirenz, lamivudine, and tenofovir disoproxil fumarate tablets in patients with persistent elevations of serum transaminases to greater than five times the upper limit of the normal range.
Discontinue efavirenz, lamivudine, and tenofovir disoproxil fumarate tablets if elevation of serum transaminases is accompanied by clinical signs or symptoms of hepatitis or hepatic decompensation.

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 should 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 (7.5)].

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 (6.1)].
(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 disoproxil fumarate [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.

5.17 **QTc Prolongation**

QTc prolongation has been observed with the use of efavirenz [see Drug Interactions (7.2, 7.5) and Clinical Pharmacology (12.2)]. Consider alternatives to efavirenz when coadministered with a drug with a known risk of Torsade de Pointes or when administered to patients at higher risk of Torsade de Pointes.

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)].
- 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)].
- Hepatotoxicity [see Warnings and Precautions (5.11)].
- Decreases in Bone Mineral Density [see Warnings and Precautions (5.14)].
- Immune Reconstitution Syndrome [see Warnings and Precautions (5.15)].
- Fat Redistribution [see Warnings and Precautions (5.16)].

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, the adverse reaction rates reported cannot be directly compared to rates in other clinical studies and may not reflect the rates observed in clinical 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 1.

Table 1 Selected Treatment-Emergent Adverse Reactionsa (Grades 2 to 4) Reported in ≥5% in Any Treatment Group in Study 903 (0 to 144 Weeks)

<table>
<thead>
<tr>
<th></th>
<th>Tenofovir disoproxil fumarate + 3TC + EFV</th>
<th>d4T + 3TC + EFV</th>
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<tr>
<td></td>
<td>N=299</td>
<td>N=301</td>
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<tr>
<td><strong>Body as a Whole</strong></td>
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<tr>
<td>Headache</td>
<td>14%</td>
<td>17%</td>
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<tr>
<td>Pain</td>
<td>13%</td>
<td>12%</td>
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<td>Fever</td>
<td>8%</td>
<td>7%</td>
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<tr>
<td>Abdominal pain</td>
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<td>12%</td>
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<tr>
<td>Back pain</td>
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<td>8%</td>
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<tr>
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<tr>
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<tr>
<td><strong>Metabolic Disorders</strong></td>
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<td>Lipodystrophyb</td>
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<td>8%</td>
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<tr>
<td><strong>Musculoskeletal</strong></td>
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<td>Arthralgia</td>
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<td>Myalgia</td>
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</table>
Nervous System

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Tenofovir Disoproxil Fumarate + 3TC + EFV</th>
<th>d4T + 3TC + EFV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>11%</td>
<td>10%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>5%</td>
<td>8%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>Peripheral neuropathy(c)</td>
<td>1%</td>
<td>5%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>6%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Respiratory

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Tenofovir Disoproxil Fumarate + 3TC + EFV</th>
<th>d4T + 3TC + EFV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>5%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Skin and Appendages

<table>
<thead>
<tr>
<th>Rash event(d)</th>
<th>Tenofovir Disoproxil Fumarate + 3TC + EFV</th>
<th>d4T + 3TC + EFV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18%</td>
<td>12%</td>
</tr>
</tbody>
</table>

- **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 4 and 5 laboratory abnormalities is provided in Table 2.

**Table 2 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)**

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Tenofovir Disoproxil Fumarate + 3TC + EFV (N = 299)</th>
<th>d4T + 3TC + EFV (N = 301)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any ≥ Grade 3 Laboratory Abnormality</td>
<td>36%</td>
<td>42%</td>
</tr>
<tr>
<td>Fasting Cholesterol (≥ 240 mg/dL)</td>
<td>19%</td>
<td>40%</td>
</tr>
<tr>
<td>Creatine Kinase (M: &gt; 990 U/L; F: &gt; 845 U/L)</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>Serum Amylase (&gt; 175 U/L)</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>AST (M: &gt; 180 U/L; F: &gt; 170 U/L)</td>
<td>5%</td>
<td>7%</td>
</tr>
<tr>
<td>ALT (M: &gt; 215 U/L; F: &gt; 170 U/L)</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Hematuria (&gt; 100 RBC/HPF)</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Neutrophils (&lt; 750/mm³)</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Fasting Triglycerides (&gt; 750 mg/dL)</td>
<td>1%</td>
<td>9%</td>
</tr>
</tbody>
</table>

**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 identified during post-approval use for each of the individual components of efavirenz, lamivudine, and tenofovir disoproxil fumarate tablets. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish causal relationship to drug exposure. These reactions have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to efavirenz, lamivudine and tenofovir disoproxil fumarate.

**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.

*Metabolic and Nutritional*: hypercholesterolemia, hypertriglyceridemia.

*Musculoskeletal*: arthralgia, myalgia, myopathy.

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

*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

7.1  Not Recommended with Other Antiretroviral Medications
Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are a complete regimen for the
treatment of HIV-1 infection; therefore, they should not be administered with other antiretroviral
medications for treatment of HIV-1 infection.

7.2  QT Prolonging Drugs
There is limited information available on the potential for a pharmacodynamic interaction
between efavirenz and drugs that prolong the QTc interval. QTc prolongation has been observed
with the use of efavirenz [see Clinical Pharmacology (12.2)]. Consider alternatives to efavirenz
when coadministered with a drug with a known risk of Torsade de Pointes.

7.3  Drugs Affecting Renal Function
Since tenofovir is primarily eliminated by the kidneys [see Clinical Pharmacology (12.3)],
coadministration of efavirenz/lamivudine/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)].

7.4  Cannabinoid Test Interaction
Efavirenz does not bind to cannabinoid receptors. False-positive urine cannabinoid test results
have been reported with some screening assays in uninfected and HIV-infected subjects receiving
efavirenz. Confirmation of positive screening tests for cannabinoids by a more specific method is
recommended.

7.5  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.

Drugs that induce CYP3A activity (e.g., phenobarbital, rifampin, rifabutin) would be expected to
increase the clearance of efavirenz resulting in lowered plasma concentrations.

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 tablets [see Clinical Pharmacology (12.3)].

Drug interactions with efavirenz are summarized in Table 3 [for pharmacokinetics data see Clinical Pharmacology (12.3, Tables 4 and 5)]. This table includes potentially significant interactions, but is not all inclusive.

### Table 3. Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

<table>
<thead>
<tr>
<th>Concomitant Drug Class: Drug Name</th>
<th>Effect</th>
<th>Clinical Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticoagulant:</strong> Warfarin</td>
<td>↑ or ↓ warfarin</td>
<td>Monitor INR and adjust warfarin dosage if necessary.</td>
</tr>
<tr>
<td><strong>Anticonvulsants:</strong> Carbamazepine</td>
<td>↓ carbamazepine* ↓ efavirenz*</td>
<td>There are insufficient data to make a dose recommendation for efavirenz. Alternative anticonvulsant treatment should be used.</td>
</tr>
<tr>
<td>Phenytoin Phenobarbital</td>
<td>↓ anticonvulsant ↓ efavirenz</td>
<td>Monitor anticonvulsant plasma levels periodically because of potential for reduction in anticonvulsant and/or efavirenz plasma levels.</td>
</tr>
<tr>
<td><strong>Antidepressants:</strong> Bupropion</td>
<td>↓ bupropion*</td>
<td>Increases in bupropion dosage should be guided by clinical response. Bupropion dose should not exceed the maximum recommended dose.</td>
</tr>
<tr>
<td>Sertraline</td>
<td>↓ sertraline*</td>
<td>Increases in sertraline dosage should be guided by clinical response.</td>
</tr>
<tr>
<td><strong>Antifungals:</strong> Itraconazole</td>
<td>↓ itraconazole* ↓ hydroxyitraconazole* ↓ ketoconazole</td>
<td>Consider alternative antifungal treatment because no dose recommendation for itraconazole or ketoconazole can be made.</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>↓ ketoconazole</td>
<td>Avoid concomitant use unless the benefit outweighs the risks.</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>↓ posaconazole*</td>
<td></td>
</tr>
<tr>
<td><strong>Anti-infective:</strong> Clarithromycin</td>
<td>↓ clarithromycin↑ 14-OH metabolite*</td>
<td>Consider alternatives to macrolide antibiotics because of the risk of QT interval prolongation.</td>
</tr>
<tr>
<td><strong>Antimycobacterial:</strong> Rifabutin</td>
<td>↓ rifabutin*</td>
<td>Increase daily dose of rifabutin by 50%. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week.</td>
</tr>
<tr>
<td><strong>Antimalarials:</strong> Artemether/lumefantrine</td>
<td>↓ artemether* ↓ dihydroartemisinin* ↓ lumefantrine*</td>
<td>Consider alternatives to artemether/lumefantrine because of the risk of QT interval prolongation.</td>
</tr>
<tr>
<td>Atovaquone/ proguanil</td>
<td>↓ atovaquone ↓ proguanil</td>
<td>Concomitant administration is not recommended.</td>
</tr>
</tbody>
</table>
### Calcium channel blockers:

**Diltiazem**
- ↓ diltiazem*
- ↓ desacetyl diltiazem*
- ↓ N-monomodesmethyldiltiazem*
- ↓ calcium channel blocker

Diltiazem dose adjustments should be guided by clinical response (refer to the full prescribing information for diltiazem).

When coadministered with efavirenz, dosage adjustment of calcium channel blocker may be needed and should be guided by clinical response (refer to the full prescribing information for the calcium channel blocker).

**Others (e.g., felodipine, nicardipine, nifedipine, verapamil)**

### HMG-CoA reductase inhibitors:

**Atorvastatin**
- ↓ atorvastatin*

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.

**Pravastatin**
- ↓ pravastatin*

**Simvastatin**
- ↓ simvastatin*

### Hepatitis C antiviral agents:

**Boceprevir**
- ↓ boceprevir*

Concomitant administration of boceprevir is not recommended.

**Elbasvir/Grazoprevir**
- ↓ elbasvir
- ↓ grazoprevir

Coadministration of efavirenz with elbasvir/grazoprevir is contraindicated [see Contraindications (4)] because it may lead to loss of virologic response to elbasvir/grazoprevir.

**Pibrentasvir/Glecaprevir**
- ↓ pibrentasvir
- ↓ glecaprevir

Coadministration of efavirenz is not recommended because it may lead to reduced therapeutic effect of pibrentasvir/glecaprevir.

**Simeprevir**
- ↓ simeprevir*
- ↔ efavirenz

Concomitant administration of simeprevir is not recommended.

**Velpatasvir/ Sofosbuvir**
- ↓ velpatasvir

Coadministration of efavirenz and sofosbuvir/velpatasvir is not recommended because it may result in loss of therapeutic effect of sofosbuvir/velpatasvir.

**Velpatasvir /Sofosbuvir/ Voxilaprevir**
- ↓ velpatasvir
- ↓ voxilaprevir

Coadministration of efavirenz and sofosbuvir/velpatasvir/voxilaprevir is not recommended because it may result in loss of therapeutic effect of sofosbuvir/velpatasvir/voxilaprevir.

**Ledipasvir/Sofosbuvir**
- ↑ tenofovir disoproxil fumarate

Monitor for adverse reactions associated with tenofovir disoproxil fumarate.

### Hepatitis B antiviral agents
Adefovir dipivoxil | Concomitant administration of adefovir dipivoxil is not recommended.

Hormonal contraceptives: |  
Oral Ethinyl estradiol/ Norgestimate  
Implant Etonogestrel  
↓ active metabolites of norgestimate*  
↓ etonogestrel | A reliable method of barrier contraception should be used in addition to hormonal contraceptives.  
A reliable method of barrier contraception should be used in addition to hormonal contraceptives. 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 | 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.

Narcotic analgesic: |  
Methadone  
↓ methadone* | Monitor for signs of methadone withdrawal and increase methadone dose if 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.

7.6 Drugs without Clinically Significant Interactions

No dosage adjustment is recommended when efavirenz, lamivudine, and tenofovir disoproxil fumarate tablets are administered with the following: aluminum/magnesium hydroxide antacids, azithromycin, cetirizine, famotidine, fluconazole, and lorazepam.

7.7 Drugs Inhibiting Organic Cation Transporters

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) [see Clinical Pharmacology (12.3)]. No data are available regarding interactions with other drugs that have renal clearance mechanisms similar to that of lamivudine.
7.8 Sorbitol

Coadministration of single doses of lamivudine and sorbitol resulted in a sorbitol dose-dependent reduction in lamivudine exposures. When possible, avoid use of sorbitol-containing medicines with lamivudine [see Warnings and Precautions (5.6), Clinical Pharmacology (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Efavirenz:

Risk Summary: There are retrospective case reports of neural tube defects in infants whose mothers were exposed to efavirenz-containing regimens in the first trimester of pregnancy. Prospective pregnancy data from the Antiretroviral Pregnancy Registry are not sufficient to adequately assess this risk. Available data from the Antiretroviral Pregnancy Registry show no difference in the risk of overall major birth defects compared to the background rate for major birth defects of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). Although a causal relationship has not been established between exposure to efavirenz in the first trimester and neural tube defects, similar malformations have been observed in studies conducted in monkeys at doses similar to the human dose. In addition, fetal and embryonic toxicities occurred in rats, at a dose ten times less than the human exposure at recommended clinical dose. Because of the potential risk of neural tube defects, efavirenz should not be used in the first trimester of pregnancy. Advise pregnant women of the potential risk to a fetus.

Data: Human Data: There are retrospective postmarketing reports of findings consistent with neural tube defects, including meningomyelocele, all in infants of mothers exposed to efavirenz-containing regimens in the first trimester.

Based on prospective reports from the Antiretroviral Pregnancy Registry (APR) of approximately 1000 live births following exposure to efavirenz-containing regimens (including over 800 live births exposed in the first trimester), there was no difference between efavirenz and overall birth defects compared with the background birth defect rate of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program. As of the interim APR report issued December 2014, the prevalence of birth defects following first-trimester exposure was 2.3% (95% CI: 1.4%-3.6%). 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. This case also included severe oblique facial clefts and amniotic banding, which have a known association with anophthalmia.

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 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, microphthalmia 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:**

*Risk Summary:* Available data from the Antiretroviral Pregnancy Registry show no difference in the risk of overall major birth defects for lamivudine compared with the background rate for major birth defects of 2.7% in the US reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). Lamivudine produced embryonic toxicity in rabbits at a dose that produced similar human exposures as the recommended clinical dose. The relevance of animal findings to human pregnancy registry data is not known.

*Data: Human Data:* Based on prospective reports from the Antiretroviral Pregnancy Registry of over 11,000 exposures to lamivudine during pregnancy resulting in live births (including over 4,300 exposed in the first trimester), there was no difference between lamivudine and overall birth defects compared with the background birth defect rate of 2.7% in the US reference population of the MACDP. The prevalence of defects in the first trimester was 3.1% (95% CI: 2.6% to 3.7%).

Lamivudine pharmacokinetics were studied in pregnant women during 2 clinical trials conducted in South Africa. The trials 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 trials 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, amniotic fluid specimens were collected following natural rupture of membranes and confirmed that lamivudine crosses the placenta in humans. Amniotic fluid concentrations of lamivudine were typically 2 times greater than maternal serum levels and ranged from 1.2 to 2.5 mcg per mL (150 mg twice daily) and 2.1 to 5.2 mcg per mL (300 mg twice daily).
**Animal Data:** Studies in pregnant rats showed that lamivudine is transferred to the fetus through the placenta. Reproduction studies with orally administered lamivudine have been performed in rats and rabbits at doses producing plasma levels up to approximately 35 times that for the recommended adult HIV dose. No evidence of teratogenicity due to lamivudine was observed. Evidence of embryo-lethality 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.

**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.

**8.2 Lactation**
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 the potential for HIV-1 transmission in breastfed infants, advise women not to breastfeed.

**Efavirenz:** Efavirenz has been shown to pass into human breast milk.

**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.

**8.3 Females and Males of Reproductive Potential**
Because of potential teratogenic effects, pregnancy should be avoided in women receiving efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. [See Use in Specific Populations (8.1).]

**Pregnancy Testing:** Females of reproductive potential should undergo pregnancy testing before initiation of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets.

**Contraception:** Females of reproductive potential should use effective contraception during treatment with efavirenz, lamivudine and tenofovir disoproxil fumarate tablets and for 12 weeks
after discontinuing efavirenz, lamivudine and tenofovir disoproxil fumarate tablets due to the long half-life of efavirenz. Barrier contraception should always be used in combination with other methods of contraception. Hormonal methods that contain progesterone may have decreased effectiveness [see Drug Interactions (7.5)].

8.4 Pediatric Use
Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should only be administered to patients with a body weight greater than or equal to 40 kg.

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, caution should be exercised in the administration of lamivudine in elderly patients reflecting 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 tablets, 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 specific treatment for overdose with lamivudine. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required 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**: 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_{9}ClF_{3}NO_{2} and its structural formula is:

![Structural formula of efavirenz](image)

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**: The chemical name of lamivudine is (-)-1-[(2R, 5S)-2-(Hydroxymethyl)-1, 3-oxathiolan-5-yl] cytosine. 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_{8}H_{11}N_{3}O_{3}S and a molecular weight of 229.3. Lamivudine has the following structural formula:
**Tenofovir:** Tenofovir disoproxil fumarate (a prodrug of tenofovir) is a fumaric acid salt of bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. Tenofovir disoproxil fumarate is converted in vivo to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate.

The chemical name is Bis (hydroxymethyl) [[(R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy] methyl] phosphonate, bis (isopropyl carbonate) (ester), fumarate (1:1); fumarate (1:1).

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. The molecular formula is C$_{19}$H$_{30}$N$_5$O$_{10}$P.C$_4$H$_4$O$_4$ and molecular weight is 635.51. Tenofovir has the following structural formula:

![Tenofovir Structural Formula](image)

Each tablet contains 600 mg of Efavirenz, 300 mg Lamivudine and 300 mg of Tenofovir Disoproxil Fumarate, which is equivalent to 245 mg of tenofovir disoproxil, and the following inactive ingredients: lactose monohydrate, croscarmellose sodium, poloxamer, hydroxypropyl cellulose, sodium lauryl sulphate, pregelatinised starch, magnesium stearate and microcrystalline cellulose. The tablets are coated with hydroxypropyl methylcellulose, lactose monohydrate, titanium dioxide, and triacetin. In this insert, all dosages are expressed in terms of Tenofovir Disoproxil Fumarate except where otherwise noted.
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 with antiviral activity against HIV-1 [see Microbiology (12.4)].

12.2 Pharmacodynamics
Cardiac Electrophysiology: The effect of efavirenz on the QTc interval was evaluated in an open-label, positive and placebo controlled, fixed single sequence 3-period, 3-treatment crossover QT study in 58 healthy subjects enriched for CYP2B6 polymorphisms. The mean C_max of efavirenz in subjects with CYP2B6 *6/*6 genotype following the administration of 600 mg daily dose for 14 days was 2.25-fold the mean C_max observed in subjects with CYP2B6 *1/*1 genotype. A positive relationship between efavirenz concentration and QTc prolongation was observed. Based on the concentration-QTc relationship, the mean QTc prolongation and its upper bound 90% confidence interval are 8.7 ms and 11.3 ms in subjects with CYP2B6*6/*6 genotype following the administration of 600 mg daily dose for 14 days [see Warnings and Precautions (5.17)].

12.3 Pharmacokinetics
The effect of food on efavirenz, lamivudine and tenofovir disoproxil fumarate tablets (600 mg/300 mg/300 mg) has not been evaluated.

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 14C-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-1-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 (t1/2) 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 disoproxil fumarate to HIV-1 infected subjects in the fasted state, maximum serum concentrations (C\text{max}) were achieved in 1.0 ± 0.4 hrs (mean ± SD) and C\text{max} and AUC values were 296 ± 90 ng/mL and 2287 ± 685 ng•hr/mL, respectively. The oral bioavailability of tenofovir from tenofovir disoproxil fumarate 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 or clinically relevant 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 or clinically relevant 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 weighing less than 40 kg.

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

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 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. 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 \( \mu M \)) 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 \( \mu M \)) only at concentrations well above those achieved clinically. 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 4 (effect of efavirenz on other drugs) and Table 5 (effect of other drugs on efavirenz). For information regarding clinical recommendations see Drug Interactions (7.5).

<table>
<thead>
<tr>
<th>Coadministered Drug</th>
<th>Dose</th>
<th>Efavirenz Dose</th>
<th>Number of Subjects</th>
<th>( C_{max} ) (mean % change)</th>
<th>AUC (mean % change)</th>
<th>( C_{min} ) (mean % change)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boceprevir</td>
<td>800 mg tid x 6 days</td>
<td>600 mg qd x 16 days</td>
<td>NA</td>
<td>↓ 8% (↓ 22-1 8%)</td>
<td>↓ 19% (11-25%)</td>
<td>↓ 44% (26-58%)</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>150 mg qd x 14 days</td>
<td>600 mg qd x 14 days</td>
<td>23</td>
<td>↓ 51% (↓ 46-56%)</td>
<td>↓ 71% (↓ 67-74%)</td>
<td>↓ 91% (↓ 88-92%)</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>600 mg single dose</td>
<td>400 mg qd x 7 days</td>
<td>14</td>
<td>↑ 22% (4-42%)</td>
<td>↔</td>
<td>NA</td>
</tr>
<tr>
<td>Clarithromycin 14-OH metabolite</td>
<td>500 mg q12h x 7 days</td>
<td>400 mg qd x 7 days</td>
<td>11</td>
<td>↓ 26% (15-35%)</td>
<td>↓ 39% (30-46%)</td>
<td>↓ 53% (42-63%)</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>200 mg x 7 days</td>
<td>400 mg qd x 7 days</td>
<td>10</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>200 mg q12h x 28 days</td>
<td>600 mg qd x 14 days</td>
<td>18</td>
<td>↓ 57% (20-51%)</td>
<td>↓ 39% (21-53%)</td>
<td>↓ 44% (27-58%)</td>
</tr>
<tr>
<td>Hydroxyitraconazole</td>
<td>400 mg (oral suspension) bid x 10 and 20 days</td>
<td>400 mg qd x 10 and 20 days</td>
<td>11</td>
<td>↓ 45% (34-53%)</td>
<td>↓ 50% (40-57%)</td>
<td>NA</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>300 mg qd x 14 days</td>
<td>600 mg qd x 14 days</td>
<td>9</td>
<td>↓ 32% (15-46%)</td>
<td>↓ 38% (28-47%)</td>
<td>↓ 45% (31-56%)</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>400 mg po q12h x 1 day, then 200 mg po q12h x 8 days</td>
<td>400 mg qd x 9 days</td>
<td>NA</td>
<td>↓ 61%*</td>
<td>↓ 77%*</td>
<td>NA</td>
</tr>
</tbody>
</table>
Table 4. Effect of Efavirenz on Coadministered Drug Plasma C_{max}, AUC, and C_{min}

<table>
<thead>
<tr>
<th>Coadministered Drug</th>
<th>Dose</th>
<th>Efavirenz Dose</th>
<th>Number of Subjects</th>
<th>Coadministered Drug (mean % change)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C_{max} (90% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AUC (90% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C_{min} (90% CI)</td>
</tr>
<tr>
<td>300 mg po q12h days 2-7</td>
<td>300 mg qd x 7 days</td>
<td>NA</td>
<td>↓ 36%(^\text{b}) (21-49%)</td>
<td>↓ 55%(^\text{b}) (45-62%)</td>
</tr>
<tr>
<td>400 mg po q12h days 2-7</td>
<td>300 mg qd x 7 days</td>
<td>NA</td>
<td>↑ 23%(^\text{b}) (1-53%)</td>
<td>↓ 7%(^\text{b}) (13%)</td>
</tr>
<tr>
<td>Artemether/ lumefantrine</td>
<td>Artemether 20 mg/ lumefantrine 120 mg tablets (6 tablet doses over 3 days)</td>
<td>600 mg qd x 26 days</td>
<td>12</td>
<td>↓ 21%</td>
</tr>
<tr>
<td>Artemether</td>
<td></td>
<td></td>
<td></td>
<td>↓ 38%</td>
</tr>
<tr>
<td>dihydroartemisinin</td>
<td></td>
<td></td>
<td></td>
<td>↔</td>
</tr>
<tr>
<td>lumefantrine</td>
<td></td>
<td></td>
<td></td>
<td>↔</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>10 mg qd x 4 days</td>
<td>600 mg qd x 15 days</td>
<td>14</td>
<td>↓ 14% (1-26%)</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>40 mg qd x 4 days</td>
<td>600 mg qd x 15 days</td>
<td>13</td>
<td>↓ 32% (5-9-12%)</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>40 mg qd x 4 days</td>
<td>600 mg qd x 15 days</td>
<td>14</td>
<td>↓ 72% (63-79%)</td>
</tr>
<tr>
<td>Total active (including metabolites)</td>
<td></td>
<td></td>
<td></td>
<td>↓ 68% (55-78%)</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>200 mg qd x 3 days, 200 mg bid x 3 days, then 400 mg qd x 29 days</td>
<td>600 mg qd x 14 days</td>
<td>12</td>
<td>↓ 20% (15-24%)</td>
</tr>
<tr>
<td>Epoxide metabolite</td>
<td></td>
<td></td>
<td></td>
<td>↔</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>10 mg single dose</td>
<td>600 mg qd x 10 days</td>
<td>11</td>
<td>↓ 24% (18-30%)</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>240 mg x 21 days</td>
<td>600 mg qd x 14 days</td>
<td>13</td>
<td>↓ 60% (50-68%)</td>
</tr>
<tr>
<td>Desacetyl diltiazem</td>
<td></td>
<td></td>
<td></td>
<td>↓ 64% (57-69%)</td>
</tr>
<tr>
<td>N-monodes-methyl diltiazem</td>
<td></td>
<td></td>
<td></td>
<td>↓ 28% (7-44%)</td>
</tr>
<tr>
<td>Ethinyl estradiol/ Norgestimate</td>
<td>0.035 mg/0.25 mg x 14 days</td>
<td>600 mg qd x 14 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethinyl estradiol</td>
<td></td>
<td></td>
<td></td>
<td>↔</td>
</tr>
<tr>
<td>Norelgestromine</td>
<td></td>
<td></td>
<td></td>
<td>↓ 46% (39-52%)</td>
</tr>
<tr>
<td>Levonorgestrel</td>
<td></td>
<td></td>
<td></td>
<td>↓ 80% (77-83%)</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>2 mg single dose</td>
<td>600 mg qd x 10 days</td>
<td>12</td>
<td>↑ 16% (2-32%)</td>
</tr>
<tr>
<td>Methadone</td>
<td>Stable maintenance 35-100 mg daily</td>
<td>600 mg qd x 14-21 days</td>
<td>11</td>
<td>↓ 45% (25-59%)</td>
</tr>
<tr>
<td>Bupropion</td>
<td>150 mg single dose (sustained-release)</td>
<td>600 mg qd x 14 days</td>
<td>13</td>
<td>↓ 34% (21-47%)</td>
</tr>
</tbody>
</table>
### Table 4. Effect of Efavirenz on Coadministered Drug Plasma C\text{max}, AUC, and C\text{min}

<table>
<thead>
<tr>
<th>Coadministered Drug</th>
<th>Dose</th>
<th>Efavirenz Dose</th>
<th>Number of Subjects</th>
<th>C\text{max} (90% CI)</th>
<th>AUC (90% CI)</th>
<th>C\text{min} (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxy-bupropion</td>
<td></td>
<td></td>
<td></td>
<td>↑ 50% (20-80%)</td>
<td>↔</td>
<td>NA</td>
</tr>
<tr>
<td>Paroxetine 20 mg qd x 14 days</td>
<td>600 mg qd x 14 days</td>
<td>16</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td></td>
</tr>
<tr>
<td>Sertraline 50 mg qd x 14 days</td>
<td>600 mg qd x 14 days</td>
<td>13</td>
<td>↓ 29% (15-40%)</td>
<td>↓ 39% (27-50%)</td>
<td>↓ 46% (31-58%)</td>
<td></td>
</tr>
</tbody>
</table>

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

a 90% CI not available.

Relative to steady-state administration of voriconazole (400 mg for 1 day, then 200 mg po q12h for 2 days).

NA = not available because of insufficient data.

### Table 5. Effect of Coadministered Drug on Efavirenz Plasma C\text{max}, AUC, and C\text{min}

<table>
<thead>
<tr>
<th>Coadministered Drug</th>
<th>Dose</th>
<th>Efavirenz Dose</th>
<th>Number of Subjects</th>
<th>C\text{max} (90% CI)</th>
<th>AUC (90% CI)</th>
<th>C\text{min} (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boceprevir 800 mg tid x 6 days</td>
<td>600 mg qd x 16 days</td>
<td>NA</td>
<td>↑ 11% (2-20%)</td>
<td>↑ 20% (15-26%)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Simeprevir 150 mg qd x 14 days</td>
<td>600 mg qd x 14 days</td>
<td>23</td>
<td>↔</td>
<td>↓ 10% (5-15%)</td>
<td>↓ 13% (7-19%)</td>
<td></td>
</tr>
<tr>
<td>Azithromycin 600 mg single dose</td>
<td>400 mg qd x 7 days</td>
<td>14</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td></td>
</tr>
<tr>
<td>Clarithromycin 500 mg q12h x 7 days</td>
<td>400 mg qd x 7 days</td>
<td>12</td>
<td>↑ 11% (3-19%)</td>
<td>↔</td>
<td>↔</td>
<td></td>
</tr>
<tr>
<td>Fluconazole 200 mg x 7 days</td>
<td>400 mg qd x 7 days</td>
<td>10</td>
<td>↔</td>
<td>↑ 16% (6-26%)</td>
<td>↑ 22% (5-41%)</td>
<td></td>
</tr>
<tr>
<td>Itraconazole 200 mg q12h x 14 days</td>
<td>600 mg qd x 28 days</td>
<td>16</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td></td>
</tr>
<tr>
<td>Rifabutin 300 mg qd x 14 days</td>
<td>600 mg qd x 14 days</td>
<td>11</td>
<td>↔</td>
<td>↔</td>
<td>↓ 12% (24-1%)</td>
<td></td>
</tr>
<tr>
<td>Rifampin 600 mg x 7 days</td>
<td>600 mg qd x 14 days</td>
<td>12</td>
<td>↓ 20% (11-28%)</td>
<td>↓ 26% (15-36%)</td>
<td>↓ 32% (15-46%)</td>
<td></td>
</tr>
<tr>
<td>Voriconazole 400 mg po q12h x 1 day, then 200 mg po q12h x 8 days</td>
<td>400 mg qd x 9 days</td>
<td>NA</td>
<td>↑ 38% (17-59%)</td>
<td>↑ 44% (29-60%)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>300 mg po q12h days 2-7</td>
<td>300 mg qd x 7 days</td>
<td>NA</td>
<td>↓ 14% (7-21%)</td>
<td>↔</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>400 mg po q12h days 2-7</td>
<td>300 mg qd x 7 days</td>
<td>NA</td>
<td>↔</td>
<td>↑ 17% (6-29%)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Artemether/ Lumefantrine Artemether 20 mg/ lumefantrine 120 mg tablets (6 4-tablet doses over 3 days)</td>
<td>600 mg qd x 26 days</td>
<td>12</td>
<td>↔</td>
<td>↓ 17%</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Atorvastatin 10 mg qd x 4 days</td>
<td>600 mg qd x 15 days</td>
<td>14</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td></td>
</tr>
<tr>
<td>Pravastatin 40 mg qd x 4 days</td>
<td>600 mg qd x 15 days</td>
<td>11</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td></td>
</tr>
</tbody>
</table>
Table 5. Effect of Coadministered Drug on Efavirenz Plasma C\text{max}, AUC, and C\text{min}

| Coadministered Drug | Dose | Efavirenz Dose | Number of Subjects | Efavirenz (mean % change) | Simvastatin
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin</td>
<td>40 mg qd x 4 days</td>
<td>600 mg qd x 15 days</td>
<td>14</td>
<td>↓ 12% (↓ 28-↑ 8%)</td>
<td>↓ 12% (↓ 25-↑ 3%)</td>
</tr>
<tr>
<td>Aluminum hydroxide</td>
<td>400 mg, magnesium hydroxide 400 mg, plus simethicone 40 mg</td>
<td>50 mL single dose</td>
<td>17</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>200 mg qd x 3 days, 200 mg bid x 3 days, then 400 mg qd x 15 days</td>
<td>600 mg qd x 35 days</td>
<td>14</td>
<td>↓ 21% (15-26%)</td>
<td>↓ 36% (32-40%)</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>10 mg single dose</td>
<td>600 mg qd x 10 days</td>
<td>11</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>240 mg x 14 days</td>
<td>600 mg qd x 28 days</td>
<td>12</td>
<td>↑ 16% (6-26%)</td>
<td>↑ 11% (5-18%)</td>
</tr>
<tr>
<td>Famotidine</td>
<td>40 mg single dose</td>
<td>400 mg single dose</td>
<td>17</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>20 mg qd x 14 days</td>
<td>600 mg qd x 14 days</td>
<td>12</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Sertraline</td>
<td>50 mg qd x 14 days</td>
<td>600 mg qd x 14 days</td>
<td>13</td>
<td>↑ 11% (6-16%)</td>
<td>↔</td>
</tr>
</tbody>
</table>

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

a 90% CI not available.
b Relative to steady-state administration of efavirenz (600 mg once daily for 9 days).
NA = not available.

Lamivudine:

Effect of Lamivudine on the Pharmacokinetics of Other Agents: Based on in vitro study results, lamivudine at therapeutic drug exposures is not expected to affect the pharmacokinetics of drugs that are substrates of the following transporters: organic anion transporter polypeptide 1B1/3 (OATP1B1/3), breast cancer resistance protein (BCRP), P-glycoprotein (P-gp), multidrug and toxin extrusion protein 1 (MATE1), MATE2-K, organic cation transporter 1 (OCT1), OCT2, or OCT3.

Effect of Other Agents on the Pharmacokinetics of Lamivudine: Lamivudine is a substrate of MATE1, MATE2-K, and OCT2 in vitro. Trimethoprim (an inhibitor of these drug transporters) has been shown to increase lamivudine plasma concentrations. This interaction is not considered clinically significant as no dose adjustment of lamivudine is needed.

Lamivudine is a substrate of P-gp and BCRP; however, considering its absolute bioavailability (87%), it is unlikely that these transporters play a significant role in the absorption of lamivudine. Therefore, coadministration of drugs that are inhibitors of these efflux transporters is unlikely to affect the disposition and elimination of lamivudine.

Interferon Alfa: There was no significant pharmacokinetic interaction between lamivudine and interferon alfa in a trial of 19 healthy male subjects [see Warnings and Precautions (5.3)].
Ribavirin: 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 subjects [see Warnings and Precautions (5.3)].

Sorbitol (Excipient): Lamivudine and sorbitol solutions were coadministered to 16 healthy adult subjects in an open-label, randomized sequence, 4-period, crossover trial. Each subject received a single 300-mg dose of lamivudine oral solution alone or coadministered with a single dose of 3.2 grams, 10.2 grams, or 13.4 grams of sorbitol in solution. Coadministration of lamivudine with sorbitol resulted in dose-dependent decreases of 20%, 39%, and 44% in the AUC(0-24), 14%, 32%, and 36% in the AUC(∞), and 28%, 52%, and 55% in the Cmax of lamivudine.

Trimethoprim/Sulfamethoxazole: Lamivudine and TMP/SMX were coadministered to 14 HIV-1-positive subjects in a single-center, open-label, randomized, crossover trial. Each subject 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. There is no information regarding the effect on lamivudine pharmacokinetics of higher doses of TMP/SMX such as those used in treat PCP.

Tenofovir Disoproxil Fumarate: At concentrations substantially higher (~300-fold) than those observed in vivo, tenofovir did not inhibit in vitro 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.

Table 6 summarizes pharmacokinetic effects of coadministered drug on tenofovir pharmacokinetics. No clinically significant drug interactions have been observed between tenofovir and methadone, oral contraceptives, or ribavirin.
Table 6. Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir\textsuperscript{a} in the Presence of the Coadministered Drug

<table>
<thead>
<tr>
<th>Coadministered Drug</th>
<th>Dose of Coadministered Drug (mg)</th>
<th>N</th>
<th>% Change of Tenofovir Pharmacokinetic Parameters\textsuperscript{b} (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>$C_{\text{max}}$</td>
</tr>
<tr>
<td>Ledipasvir/ Sofosbuvir\textsuperscript{ef}</td>
<td>90/400 once daily x 10 days</td>
<td>24</td>
<td>↑ 47 (↑ 37 to ↑ 58)</td>
</tr>
<tr>
<td>Ledipasvir/ Sofosbuvir\textsuperscript{eg}</td>
<td>90/400 once daily x 10 days</td>
<td>23</td>
<td>↑ 64 (↑ 54 to ↑ 74)</td>
</tr>
<tr>
<td>Ledipasvir/Sofosbuvir\textsuperscript{c}</td>
<td>90/400 once daily x 14 days</td>
<td>15</td>
<td>↑ 79 (↑ 56 to ↑ 104)</td>
</tr>
<tr>
<td>Sofosbuvir\textsuperscript{d}</td>
<td>400 single dose</td>
<td>16</td>
<td>↑ 25 (↑ 8 to ↑ 45)</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>0.05 mg/kg twice daily x 7 days</td>
<td>21</td>
<td>↑ 13 (↑ 1 to ↑ 27)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Subjects received tenofovir disoproxil fumarate 300 mg once daily.

\textsuperscript{b} Increase = ↑; Decrease = ↓; No Effect = ⇄; NC = Not Calculated

\textsuperscript{c} Study conducted with efavirenz/emtricitabine/tenofovir disoproxil fumarate coadministered with ledipasvir/sofosbuvir.

d Study conducted with efavirenz/emtricitabine/tenofovir disoproxil fumarate coadministered with sofosbuvir.

e Data generated from simultaneous dosing with HARVONI (ledipasvir/sofosbuvir). Staggered administration (12 hours apart) provide similar results.

f Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine/tenofovir DF.

g Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/tenofovir DF.

No effect on the pharmacokinetic parameters of tacrolimus was observed when coadministered with tenofovir disoproxil fumarate.

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 $\alpha$, $\beta$, $\gamma$, and $\delta$ are not inhibited by efavirenz.

Lamivudine: Lamivudine is a synthetic nucleoside analogue with activity against HIV-1 and HBV. 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 HIV-1 reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue.

Tenofovir Disoproxil Fumarate: Tenofovir disoproxil fumarate is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir disoproxil fumarate requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase and HBV reverse transcriptase 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<sub>90</sub> to EC<sub>95</sub>) 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. The anti-HIV-1 activity of efavirenz in combination with the NNRTIs delavirdine and nevirapine, NRTIs (abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine, zidovudine), PIs (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir), and the fusion inhibitor enfuvirtide was not antagonistic in cell culture.

*Lamivudine:* The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes (PBMCs) using standard susceptibility assays. EC<sub>50</sub> values were in the range of 3 to 15,000 nM. (1 μM = 0.23 mcg/mL). The median EC<sub>50</sub> values of lamivudine were 60 nM (range: 20 to 70 nM), 35 nM (range: 30 to 40 nM), 30 nM (range: 20 to 90 nM), 20 nM (range: 3 to 40 nM), 30 nM (range: 1 to 60 nM), 30 nM (range: 20 to 70 nM), 30 nM (range: 3 to 70 nM), and 30 nM (range: 20 to 90 nM) against HIV-1 clades A-G and group O viruses (n = 3 except n = 2 for clade B), respectively. The EC<sub>50</sub> values against HIV-2 isolates (n = 4) ranged from 3 to 120 nM in PBMCs. Lamivudine was not antagonistic to all tested anti-HIV agents. Ribavirin (50 microM) used in the treatment of chronic HCV infection decreased the anti-HIV-1 activity of lamivudine by 3.5 fold in MT-4 cells.

*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<sub>50</sub> (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). Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC<sub>50</sub> values ranged from 0.5 μM to 2.2 μM) and strain specific activity against HIV-2 (EC<sub>50</sub> values ranged from 1.6 μM to 5.5 μM). Please see the full prescribing information for VIREAD for information regarding the inhibitory activity of lamivudine against HBV.

**Resistance**

*Efavirenz:* In cell culture, HIV-1 isolates with reduced susceptibility to efavirenz (> 380-fold increase in EC<sub>90</sub> 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 reverse transcriptase.
Clinical isolates with reduced susceptibility in cell culture to efavirenz have been obtained. One or more RT substitutions at amino acid positions A98, L100, K101, K103, V106, V108, Y188, G190, P225, F227 and M230 were observed in patients failing treatment with efavirenz in combination with indinavir, or with lamivudine plus zidovudine. The K103N substitution was the most frequently observed.

Lamivudine: Lamivudine-resistant variants of HIV-1 have been selected in cell culture. Genotypic analysis showed that resistance was predominantly due to a methionine to valine or isoleucine (M184V/I) substitution in reverse transcriptase.

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 addition, a K70E substitution in HIV-1 reverse transcriptase has been selected by tenofovir and results in low-level reduced susceptibility to tenofovir. K65R substitutions developed in some subjects failing a tenofovir disoproxil fumarate regimen.

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

Lamivudine: Cross-resistance among NRTIs has been observed. Lamivudine-resistant HIV-1 isolates were cross-resistant in cell culture to didanosine (ddl). Cross-resistance is also expected with abacavir and emtricitabine as these select M184V substitutions.

Tenofovir Disoproxil Fumarate: Cross-resistance among NRTIs has been observed. The K65R and K70E substitutions selected by tenofovir are also selected in some HIV-1 infected subjects treated with abacavir or didanosine. HIV-1 isolates with the K65R substitution also showed reduced susceptibility to emtricitabine and lamivudine. 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) the human exposures at the recommended dose of 300 mg. Lamivudine was not mutagenic in a microbial mutagenicity assay, in an in vitro cell transformation assay, in a rat micronucleus test, in a rat bone marrow cytogenetic assay, and in assay for unscheduled DNA synthesis in rat liver. Lamivudine showed no evidence of in vivo genotoxic activity in the rat at oral doses of up to 2000 mg per 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 per kg per 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...
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)].

**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/mm³ (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/mm³. Treatment outcomes through 48 and 144 weeks are presented in Table 7.
Table 7 Outcomes of Randomized Treatment at Week 48 and 144 (Study 903)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>At Week 48</th>
<th>At Week 144</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tenofovir disoproxil fumarate+3TC +EFV (N=299)</td>
<td>d4T+3TC +EFV (N=301)</td>
</tr>
<tr>
<td>Respondera</td>
<td>79%</td>
<td>82%</td>
</tr>
<tr>
<td>Virologic failureb</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Rebound</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Never suppressed</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Added an antiretroviral agent</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Death</td>
<td>&lt;1%</td>
<td>1%</td>
</tr>
<tr>
<td>Discontinued due to adverse event</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Discontinued for other reasonsc</td>
<td>8%</td>
<td>7%</td>
</tr>
</tbody>
</table>

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 \( \leq 100,000 \) copies/mL) and CD4+ cell count (< or \( \geq 200 \) cells/mm³). 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/mm³ for the tenofovir disoproxil fumarate arm and 283 cells/mm³ 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 600mg/300mg/300mg White to off-white, capsule shaped, biconvex, film-coated tablets debossed 'M 9' on one side of the tablet and having plain surface on the other side.

Bottle of 30 tablets with silica gel desiccant and induction seal - NDC 33342-227-07
Bottle of 90 tablets with silica gel desiccant and induction seal - NDC 33342-227-10
Bottle of 100 tablets with silica gel desiccant and induction seal - NDC 33342-227-57
Bottle of 180 tablets with silica gel desiccant and induction seal - NDC 33342-227-11

Store at room temperature below 30°C (86°F)
17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

Information for Patients
Patients should be advised that efavirenz, lamivudine and tenofovir disoproxil fumarate tablets:

- 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.
- are 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 tablets.
- Patients should avoid doing things that can spread HIV-1 infection to others.
  - Do not share or reuse 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 safer 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 tablets are unknown.
- Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are for oral ingestion only.
- Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should not be discontinued without first informing their physician.
- It is important to take efavirenz, lamivudine and tenofovir disoproxil fumarate tablets 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 tablets 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, components of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets [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
In patients with chronic hepatitis B, it is important to obtain HIV antibody testing prior to initiating lamivudine and tenofovir disoproxil fumarate, components of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets.

Renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported. Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should be avoided with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple NSAIDs) and 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 [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 tablets [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, psychosis-like symptoms and catatonia have been reported in patients receiving efavirenz [see Warnings and Precautions (5.7)]. If they experience severe psychiatric adverse experiences they should seek immediate medical evaluation. Patients should be advised to inform their physician of any history of mental illness or substance abuse.

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.

Inform patients to watch for early warning signs of liver inflammation or failure, such as fatigue, weakness, lack of appetite, nausea and vomiting, as well as later signs such as jaundice, confusion, abdominal swelling, and discolored feces, and to consult their health care professional without delay if such symptoms occur [see Warnings and Precautions (5.9) and Adverse Reactions (6.1)].

Advise females of reproductive potential to use effective contraception as well as a barrier method during treatment with efavirenz, lamivudine and tenofovir disoproxil fumarate tablets and for 12 weeks after discontinuation of use. Advise patients to contact their healthcare provider if they plan to become pregnant, become pregnant, or if pregnancy is suspected during treatment with efavirenz, lamivudine and tenofovir disoproxil fumarate tablets.

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should not be administered in combination with HEPSERA (adefovir dipivoxil) [see Warnings and Precautions (5.3)].

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets 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 tablets, 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 tablets, and that the cause and long-term health effects of these conditions
are not known at this time [see Warnings and Precautions (5.16)].

- In some patients with advanced HIV infection, signs and symptoms of inflammation from
previous infections may occur soon after anti-HIV treatment is started. It is believed that
these symptoms are due to an improvement in the body's immune response, enabling the
body to fight infections that may have been present with no obvious symptoms. Advise
patients to inform their healthcare provider immediately of any symptoms of infection [see
Warnings and Precautions (5.15)].

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Rx only

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Manufactured for:
Macleods Pharma USA, Inc.
Plainsboro, NJ 08536

Manufactured by:
Macleods Pharmaceuticals Ltd.
Baddi, Himachal Pradesh, 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 tablets 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 tablets?

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets 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 tablets 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 tablets 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 tablets 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 tablets. 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 mental health problems.** Tell your doctor right away if you have any of the following symptoms:

• feel sad or hopeless
• feel anxious or restless
• have thoughts of hurting yourself (suicide) or have tried to hurt yourself or others
• are not able to tell the difference between what is true or real and what is false or unreal
• do not trust other people
• hear or see things that are not real
• are not able to move or speak normally

**What are efavirenz, lamivudine and tenofovir disoproxil fumarate tablets?**

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are a prescription medicine used:

• alone as a complete regimen to treat Human Immunodeficiency Virus (HIV) in patients weighing at least 40 kg. HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome). Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets do not cure HIV or AIDS. People taking efavirenz, lamivudine and tenofovir disoproxil fumarate tablets 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.

**Who should not take efavirenz, lamivudine and tenofovir disoproxil fumarate tablets?**

• Do not take efavirenz, lamivudine, and tenofovir disoproxil fumarate tablets if you are allergic to any of the ingredients in the tablet. See the end of this leaflet for a complete list of ingredients.
• Do not take efavirenz, lamivudine, and tenofovir disoproxil fumarate tablets if you are currently taking elbasvir and grazoprevir.
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 a heart condition
- 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 tablets and for 12 weeks after stopping it. If you are able to become pregnant, your healthcare provider should do a pregnancy test before you start efavirenz, lamivudine and tenofovir disoproxil fumarate tablets.
- 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 tablets may affect the way other medicines work, and other medicines may affect how efavirenz, lamivudine and tenofovir disoproxil fumarate tablets work.

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 tablets?

- See “What is the most important information I should know about efavirenz, lamivudine and tenofovir disoproxil fumarate tablets?”
- Take efavirenz, lamivudine and tenofovir disoproxil fumarate tablets exactly as your healthcare provider tells you to take them.
- Take efavirenz, lamivudine and tenofovir disoproxil fumarate tablets 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 tablets.
- 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 tablets. 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 tablets, do not take the missed dose. Take the next dose at your regular time.
- If you take too many efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, 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 tablets?

- **See “What is the most important information I should know about efavirenz, lamivudine and tenofovir disoproxil fumarate tablets?”**
- **New or worse kidney problems** can happen in some people who take efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. 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 tablets.
- **Bone problems** can happen in some people who take efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. 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 tablets.

Liver problems, including liver failure and death can happen in people who take efavirenz, a component of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. Liver problems can happen in people without a history of liver problems. Your doctor will do blood tests to check your liver before you start efavirenz, lamivudine and tenofovir disoproxil fumarate tablets and during treatment. Tell your doctor right away if you get any of the following symptoms:

- your skin or the white part of your eyes turns yellow (jaundice)
- you don’t feel like eating food for several days or longer
- you feel sick to your stomach (nausea)
- your urine turns dark
- your bowel movements (stools) turn light in color
- you have lower stomach area (abdominal) pain

The most common side effects of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are:
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 tablets. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store efavirenz, lamivudine and tenofovir disoproxil fumarate tablets?

- Store efavirenz, lamivudine and tenofovir disoproxil fumarate tablets below 30°C (86°F).
- 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 tablets
Medicines are sometimes prescribed for purposes other than those listed in the patient leaflet. Do not use efavirenz, lamivudine and tenofovir disoproxil fumarate tablets for a condition for which they were not prescribed. Do not give efavirenz, lamivudine and tenofovir disoproxil fumarate tablets to other people, even if they have the same condition you have. They may harm them.

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets do 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 efavirenz, 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 tablets that is written for health professionals.

What are the ingredients in efavirenz, lamivudine and tenofovir disoproxil fumarate tablets?

Active Ingredients: Efavirenz, Lamivudine, Tenofovir disoproxil fumarate

Inactive Ingredients: lactose monohydrate, croscarmellose sodium, poloxamer, hydroxypropyl cellulose, sodium lauryl sulphate, pregelatinised starch, magnesium stearate and microcrystalline cellulose. The tablets are coated with hydroxypropyl methylcellulose, lactose monohydrate, titanium dioxide, and triacetin.

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