

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EFAVIRENZ, LAMIVUDINE and TENOFOVIR DISOPROXIL FUMARATE tablets safely and effectively. See full prescribing information for EFAVIRENZ, LAMIVUDINE and TENOFOVIR DISOPROXIL FUMARATE tablets.

EFAVIRENZ, LAMIVUDINE and TENOFOVIR DISOPROXIL FUMARATE tablets, for oral use

Initial U.S. Approval: 2019

WARNING: POST TREATMENT ACUTE EXACERBATIONS OF HEPATITIS B

See full prescribing information for complete boxed warning.

Severe acute exacerbations of hepatitis B virus (HBV) have been reported in HBV-infected patients who have discontinued anti-HBV therapy, including lamivudine or tenofovir disoproxil fumarate, two components of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. Monitor hepatic function closely in HBV-infected patients who discontinue efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. If appropriate, initiation of anti-HBV therapy may be warranted. (5.1)

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

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets is three-drug combination of efavirenz (EFV), a non-nucleoside reverse transcriptase inhibitor, and lamivudine and tenofovir disoproxil fumarate, both nucleoside reverse transcriptase inhibitors and is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients weighing at least 35 kg. (1)

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

- Testing: Prior to or when initiating efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, test for HBV infection. Prior to initiation and during use of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus. (2.1)
- Recommended dose in adults and pediatric patients weighing at least 35 kg: One tablet once daily orally on an empty stomach, preferably at bedtime. (2.2)
- Renal Impairment: Not recommended in patients with CrCL less than 50 mL/min or patients with end-stage renal disease requiring hemodialysis. (2.3)
- Hepatic Impairment: Not recommended for patients with moderate or severe hepatic impairment. Use caution in patients with mild hepatic impairment. (2.4)

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

Tablets: 400 mg of efavirenz, 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate. (3)

-----CONTRAINDICATIONS-----

- Previous hypersensitivity reaction (e.g., Stevens Johnson syndrome, erythema multiforme, or toxic skin eruptions) to efavirenz, lamivudine, or tenofovir disoproxil fumarate. (4)
- Coadministration with elbasvir/grazoprevir. (4)

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

- Risk of adverse reactions or loss of virologic response due to drug interactions: Consult full prescribing information prior to and during treatment for important potential drug interactions. Consider alternatives to efavirenz, lamivudine and tenofovir disoproxil fumarate tablets in patients taking other medications with a known risk of Torsade de Pointes or in patients at higher risk of Torsade de Pointes. (5.2)
- New onset or worsening renal impairment: Can include acute renal failure and Fanconi syndrome. Assess estimated creatinine clearance before initiating treatment with efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. In patients at risk for renal dysfunction, assess estimated creatinine clearance, serum phosphorus, urine glucose and urine protein

before initiating treatment with efavirenz, lamivudine and tenofovir disoproxil fumarate tablets and periodically during treatment. Avoid administering efavirenz, lamivudine and tenofovir disoproxil fumarate tablets with concurrent or recent use of nephrotoxic drugs. (5.3)

- Serious psychiatric symptoms: Immediate medical evaluation is recommended for serious psychiatric symptoms such as severe depression or suicidal ideation. (5.4, 17)
- Nervous system symptoms (NSS): NSS are frequent, usually begin 1 to 2 days after initiating therapy and resolve in 2 to 4 weeks. Dosing at bedtime may improve tolerability. NSS are not predictive of onset of psychiatric symptoms. (5.5, 17)
- Embryo-Fetal Toxicity: Avoid administration in the first trimester of pregnancy as fetal harm may occur. (5.6, 8.1)
- Rash: Rash usually begins within 1 to 2 weeks after initiating therapy and resolves within 4 weeks. Discontinue if severe rash develops. (5.7, 17)
- Hepatotoxicity: Monitor liver function tests before and during treatment in patients with underlying hepatic disease, including hepatitis B or C coinfection, marked transaminase elevations, or who are taking medications associated with liver toxicity. Among reported cases of hepatic failure, a few occurred in patients with no pre-existing hepatic disease. (5.8, 8.7)
- Hepatic decompensation, some fatal, has occurred in HIV-1/HCV co-infected patients receiving interferon and ribavirin-based regimens. Monitor for treatment-associated toxicities. Discontinue efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, as medically appropriate and consider dose reduction or discontinuation of interferon alfa, ribavirin, or both. (5.9)
- Pancreatitis: Use with caution in pediatric patients with a history of pancreatitis or other significant risk factors for pancreatitis. Discontinue treatment as clinically appropriate. (5.10)
- Convulsions: Use caution in patients with a history of seizures. (5.11)
- Lipids: Total cholesterol and triglyceride elevations. Monitor before therapy and periodically thereafter. (5.12)
- Decreases in bone mineral density (BMD): Consider assessment of BMD in patients with a history of pathologic fracture or other risk factors for osteoporosis or bone loss. (5.13)
- Immune reconstitution syndrome: Observed in HIV-infected patients. May necessitate further evaluation and treatment. (5.14)
- Lactic acidosis and severe hepatomegaly with steatosis: Discontinue treatment in patients who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity. (5.15)

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

- Most common adverse reactions (> 5% with efavirenz, lamivudine and tenofovir disoproxil fumarate tablets) are rash and dizziness. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Macleods Pharma USA, Inc., at 1-888-943-3210 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should not be administered with other antiretroviral medications for the treatment of HIV-1 infection. (7.1)
- Coadministration 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 tablets. The potential for drug-drug interactions should be considered before and during therapy. (5.2, 7)

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

- Pregnancy: Women should avoid pregnancy during EFV therapy, a component of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, and for 12 weeks after discontinuation. (5.6)
- Lactation: Breastfeeding not recommended due to potential for HIV transmission. (8.2)
- Females and Males of Reproductive Potential: Pregnancy testing and contraception are recommended. (8.3)

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

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FULL PRESCRIBING INFORMATION

WARNING: POST TREATMENT ACUTE EXACERBATIONS OF HEPATITIS B

Severe acute exacerbations of hepatitis B virus (HBV) have been reported in HBV-infected patients who have discontinued anti-HBV therapy, including lamivudine and tenofovir disoproxil fumarate, two components of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in HBV-infected patients who discontinue efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. If appropriate, initiation of anti-hepatitis B therapy may be warranted [see *Warnings and Precautions (5.1)*].

1 INDICATIONS AND USAGE

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients weighing at least 35 kg.

2 DOSAGE AND ADMINISTRATION

2.1 Testing Prior to Initiation and During Treatment with Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets

Prior to or when initiating efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, test patients for hepatitis B virus (HBV) infection [see *Warnings and Precautions (5.1)*].

Prior to initiation and during treatment with efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus. [see *Warnings and Precautions (5.3)*].

2.2 Recommended Dosage

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets is a fixed-dose combination product containing 400 mg of efavirenz (EFV), 300 mg of lamivudine (3TC), and 300 mg of tenofovir disoproxil fumarate (TDF). The recommended dosage regimen of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets in adults and pediatric patients weighing at least 35 kg (77 lb) is one tablet once daily orally. Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should be taken on an empty stomach, preferably at bedtime. Dosing at bedtime may improve the tolerability of nervous system symptoms [see *Warnings and Precautions (5.5) and Adverse Reactions (6.1)*].

2.3 Not Recommended in Renal Impairment

Because efavirenz, lamivudine and tenofovir disoproxil fumarate tablets is a fixed-dose combination product and cannot be dose adjusted, it is not recommended for patients requiring dosage adjustment, patients with creatinine clearance less than 50 mL per min, or patients with end-stage renal disease (ESRD) requiring hemodialysis [see *Use in Specific Populations (8.6)*].

2.4 Not Recommended in Moderate to Severe Hepatic Impairment

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh B or C) [see *Warnings and Precautions (5.8) and Use in Specific Populations (8.7)*].

3 DOSAGE FORMS AND STRENGTHS

Efavirenz, lamivudine and tenofovir disoproxil fumarate film-coated tablets are pink colored, capsule shaped, biconvex, film coated tablets debossed with "F 31" on one side and plain on the other side containing 400 mg of efavirenz, 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets is contraindicated in patients:

- with prior hypersensitivity reaction (e.g., Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to efavirenz [see *Warnings and Precautions (5.7)*], lamivudine, or tenofovir disoproxil fumarate.
- when coadministered with elbasvir and grazoprevir [see *Warnings and Precautions (5.2)* and *Drug Interactions (7.5)*].

5 WARNINGS AND PRECAUTIONS

5.1 Severe Acute Exacerbation of Hepatitis B in Patients with HBV Infection

All patients should be tested for the presence of chronic hepatitis B virus (HBV) before or when initiating efavirenz, lamivudine, and tenofovir disoproxil fumarate tablets.

Discontinuation of anti-HBV therapy, including 3TC and TDF, two components of efavirenz, lamivudine, and tenofovir disoproxil fumarate tablets, may be associated with severe acute exacerbations of hepatitis B. Patients infected with HBV who discontinue efavirenz, lamivudine, and tenofovir disoproxil fumarate tablets 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.

5.2 Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions

The concomitant use of efavirenz, lamivudine, and tenofovir disoproxil fumarate tablets and other drugs may result in known or potentially significant drug interactions, some of which may lead to [see *Contraindications (4)* and *Drug Interactions (7.5)*]:

- Loss of therapeutic effect of efavirenz, lamivudine, and tenofovir disoproxil fumarate tablets and possible development of resistance.
- Possible clinically significant adverse reactions from greater exposures of concomitant drugs.

QTc prolongation has been observed with the use of EFV [see *Drug Interactions (7.2, 7.5)* and *Clinical Pharmacology (12.2)*], a component of efavirenz, lamivudine, and tenofovir disoproxil fumarate tablets. Consider alternatives to efavirenz, lamivudine, and tenofovir disoproxil fumarate tablets 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.

See Table 5 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during therapy with efavirenz, lamivudine, and tenofovir disoproxil fumarate tablets; review concomitant medications during therapy with efavirenz, lamivudine, and tenofovir disoproxil fumarate tablets therapy; and monitor for the adverse reactions associated with the concomitant drugs.

5.3 New Onset or Worsening Renal Impairment

TDF, 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 TDF [see *Adverse Reactions (6.2)*].

Prior to initiation and during use of efavirenz, lamivudine, and tenofovir disoproxil fumarate tablets, on a clinically appropriate schedule, assess serum creatine, estimated creatine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus.

Avoid efavirenz, lamivudine and tenofovir disoproxil fumarate tablets with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs)) [see *Drug Interactions (7.7)*]. Cases of acute renal failure after initiation of high dose or multiple NSAIDs have been reported in HIV-infected patients with risk factors for renal dysfunction who appeared stable on TDF. 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.

5.4 Psychiatric Symptoms

Serious psychiatric adverse experiences have been reported in patients treated with EFV, a component of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. In controlled trials of 1008 patients treated with regimens containing EFV 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 EFV 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 a study using EFV 600 mg, treatment with EFV was associated with an increase in the occurrence of these selected psychiatric symptoms. Other factors associated with an increase in the occurrence of these psychiatric symptoms were history of injection drug use, psychiatric history, and receipt of psychiatric medication at study entry; similar associations were observed in both the EFV and control treatment groups. In a study using EFV 600 mg, onset of new serious psychiatric symptoms occurred throughout the study for both efavirenz-treated and control-treated patients. One percent of EFV-treated patients discontinued or interrupted treatment because of one or more of these selected psychiatric symptoms.

In the ENCORE1 (Evaluation of Novel Concepts in Optimization of antiRetroviral Efficacy) Trial, at Week 48 the frequency (regardless of causality) of the most common (occurring in > 1% patients) psychiatric events among patients who received EFV 400 mg (N = 321) or EFV 600 mg (N = 309) regimens, respectively, were: abnormal dreams (8.7%, 11.3%), insomnia (6.2%, 6.5%), somnolence (3.1%, 3.9%), depression (3.1%, 1.6%), nightmare (1.9%, 2.6%), sleep disorder (2.2%, 1.3%), and anxiety (1.2%, 1.3%).

There have also been occasional postmarketing reports of death by suicide, delusions, and psychosis-like behavior, although a causal relationship to the use of EFV cannot be determined from these reports [see *Adverse Reactions* (6.2)]. 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 EFV, and if so, to determine whether the risks of continued therapy outweigh the benefits.

5.5 Nervous System Symptoms

Fifty-three percent (531/1008) of patients receiving EFV, 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 EFV and from 3% to 5% in patients treated with a control regimen. Inform patients 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* (5.4)]. Dosing at bedtime may improve the tolerability of these nervous system symptoms [see *Dosage and Administration* (2.2)].

In the ENCORE1 Trial, at Week 48, 40% of EFV 400 mg recipients and 48% of EFV 600 mg recipients reported central nervous system disorders. The most common symptoms (> 10%) were dizziness (27% vs. 35%) and headache (11% vs. 11%).

5.6 Embryo-Fetal Toxicity

EFV, 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 EFV to avoid pregnancy [see *Use in Specific Populations* (8.1, 8.3)].

5.7 Skin and Systemic Hypersensitivity Reaction

In controlled clinical trials, 26% (266/1008) of patients treated with EFV 600 mg experienced new-onset skin rash compared with 17% (111/635) of patients treated in control groups. Rash associated with blistering, moist desquamation, or ulceration occurred in 0.9% (9/1008) of patients treated with EFV. The incidence of Grade 4 rash (e.g., erythema multiforme, Stevens-Johnson syndrome) in patients treated with EFV 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 EFV (median time to onset of rash in adults was 11 days) and, in most patients continuing therapy with EFV, rash resolves within 1 month (median duration, 16 days). The discontinuation rate for rash in clinical trials was 1.7% (17/1008).

EFV can generally be reinitiated in patients interrupting therapy because of rash. EFV 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 (e.g., Stevens-Johnson syndrome), alternate therapy should be considered [see *Contraindications* (4)].

In the ENCORE1 Trial at Week 48, different types of rash (such as rash, rash papular, rash maculopapular and rash pruritic) occurred in 32% of EFV 600 mg recipients and 26% of EFV 400 mg recipients. Grade 3-4 rash was reported in 3% of EFV 600 mg recipients and 1% of EFV 400 mg recipients. The discontinuation rate for rash in the ENCORE1 Trial was 3% of EFV 600 mg recipients and 1% of EFV 400 mg recipients.

5.8 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 EFV. 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.

EFV, a component of efavirenz, lamivudine, and tenofovir disoproxil fumarate tablets, is not recommended for patients with moderate or severe hepatic impairment. Careful monitoring is recommended for patients with mild hepatic impairment receiving EFV [see *Adverse Reactions (6.1)* and *Use in Specific Populations (8.7)*].

Monitoring of liver enzymes before and during treatment is recommended for all patients [see *Dosage and Administration (2.4)*]. 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.

5.9 Risk of Hepatic Decompensation When Used with Interferon- and Ribavirin-Based Regimens

In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as 3TC, 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 3TC 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 3TC should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of efavirenz, lamivudine, and tenofovir disoproxil fumarate tablets should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Child-Pugh >6). See the complete prescribing information for interferon and ribavirin.

5.10 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, 3TC, a component of efavirenz, lamivudine, and tenofovir disoproxil fumarate tablets, 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 [see *Adverse Reactions (6.1)*].

5.11 Convulsions

Convulsions have been observed in patients receiving EFV, a component of efavirenz, lamivudine, and tenofovir disoproxil fumarate tablets, generally in the presence of known medical history of seizures [see *Nonclinical Toxicology (13.2)*]. Caution must be taken in any patient with a history of seizures. Patients who are receiving concomitant anticonvulsant medications primarily metabolized by the liver, such as phenytoin and phenobarbital, may require periodic monitoring of plasma levels [see *Drug Interactions (7.5)*].

5.12 Lipid Elevations

Treatment with EFV, a component of efavirenz, lamivudine, and tenofovir disoproxil fumarate tablets, has resulted in increases in the concentration of total cholesterol and triglycerides. Cholesterol and triglyceride testing should be performed before initiating therapy with efavirenz, lamivudine, and tenofovir disoproxil fumarate tablets and at periodic intervals during therapy.

5.13 Bone Loss and Mineralization Defects

Bone Mineral Density

In clinical trials in HIV-1 infected adults, TDF, a component of efavirenz, lamivudine, and tenofovir disoproxil fumarate tablets, 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 TDF.

Clinical trials evaluating TDF in pediatric subjects were conducted. Under normal circumstances, BMD increases rapidly in pediatric patients. In HIV-1 infected subjects 2 years to less than 18 years of age, bone effects were similar to those observed in adult subjects

and suggest increased bone turnover. Total body BMD gain was less in the TDF-treated HIV-1 infected pediatric subjects as compared to the control groups. Similar trends were observed in HBV-infected subjects 12 years to less than 18 years of age. In all pediatric trials, skeletal growth (height) appeared to be unaffected for the duration of the clinical trials.

The effects of TDF-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk in adults and pediatric subjects 2 years and older are unknown. The long-term effect of lower spine and total body BMD on skeletal growth in pediatric patients, and in particular, the effects of long-duration exposure in younger children is unknown. 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. Assessment of BMD should be considered for adult and pediatric patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. If bone abnormalities are suspected, 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 TDF [see *Adverse Reactions (6.2)*]. Arthralgias and muscle pain or weakness have also been reported in cases of proximal renal tubulopathy. Hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving products containing TDF [see *Warnings and Precautions (5.3)*].

5.14 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including the components of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. 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.

5.15 Lactic Acidosis and Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues, including 3TC and TDF, two components of efavirenz, lamivudine, and tenofovir disoproxil fumarate tablets, alone or in combination with other antiretrovirals. Treatment with efavirenz, lamivudine, and tenofovir disoproxil fumarate tablets should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

6 ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of the labeling:

- Exacerbations of Hepatitis B [see *Boxed Warning, Warnings and Precautions (5.2)*].
- New Onset or Worsening Renal Impairment [see *Warnings and Precautions (5.3)*].
- Psychiatric Symptoms [see *Warnings and Precautions (5.4)*].
- Nervous System Symptoms [see *Warnings and Precautions (5.5)*].
- Skin and Systemic Hypersensitivity Reaction [see *Warnings and Precautions (5.7)*].
- Hepatotoxicity [see *Warnings and Precautions (5.8)*].
- Hepatic Decompensation in Patients Co-infected with HIV-1 and Hepatitis C [see *Warnings and Precautions (5.9)*].
- Pancreatitis [see *Warnings and Precautions (5.10)*].
- Bone Loss and Mineralization Defects [see *Warnings and Precautions (5.13)*].
- Immune Reconstitution Syndrome [see *Warnings and Precautions (5.14)*].
- Lactic Acidosis and Severe Hepatomegaly with Steatosis [see *Warnings and Precautions (5.15)*].

6.1 Clinical Trials Experience

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

Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate

In Trial 903, 600 antiretroviral-naïve subjects received TDF (N=299) or stavudine (d4T) (N=301) administered in combination with 3TC and EFV for 144 weeks. The most common adverse reactions 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. Table 1 provides the treatment-emergent adverse reactions (Grades 2-4) occurring in greater than or equal to 5% of subjects treated in any treatment group.

Table 1 Selected Adverse Reactions^a (Grades 2–4) Reported in ≥5% in Any Treatment Group in Trial 903 (0–144 Weeks)

	TDF+3TC+EFV	d4T+3TC+EFV
	N=299	N=301
Rash event ^b	18%	12%
Headache	14%	17%
Pain	13%	12%
Diarrhea	11%	13%
Depression	11%	10%
Back pain	9%	8%
Nausea	8%	9%
Fever	8%	7%
Abdominal pain	7%	12%
Asthenia	6%	7%
Anxiety	6%	6%
Vomiting	5%	9%
Insomnia	5%	8%
Arthralgia	5%	7%
Pneumonia	5%	5%
Dyspepsia	4%	5%
Dizziness	3%	6%
Myalgia	3%	5%
Lipodystrophy ^c	1%	8%
Peripheral neuropathy ^d	1%	5%

- a. Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.
- b. Rash event includes rash, pruritus, maculopapular rash, urticaria, vesicubullous rash, and pustular rash.
- c. Lipodystrophy represents a variety of investigator-described adverse events not a protocol-defined syndrome.
- d. Peripheral neuropathy includes peripheral neuritis and neuropathy.

ENCORE1 Trial - Adverse Reactions: The most common adverse reactions seen in a double-blind comparative controlled trial in which 630 treatment-naïve subjects received EFV 400 mg (N = 321) or EFV 600 mg (N = 309) in combination with fixed-dose emtricitabine (FTC)/TDF for 48 weeks were mild to moderate gastrointestinal events, dizziness, abnormal dreams, and rash. Table 2 provides selected clinical adverse reactions of moderate or severe intensity occurring in greater than or equal to 2% of treatment-naïve subjects receiving combination therapy including EFV 400 mg or EFV 600 mg.

Table 2 Selected Adverse Reactions^a(Grades 2-4) Reported in ≥ 2% in Either Treatment Group in the ENCORE1 Trial through Week 48

	EFV 400 mg + FTC/TDF	EFV 600 mg + FTC/TDF
	N = 321	N = 309
Rash event ^b	9%	13%
Dizziness	6%	9%
Insomnia	3%	4%
Abnormal dreams	2%	2%
Headache	1%	3%
Diarrhea	2%	3%
Vomiting	1%	2%
Pyrexia	2%	1%
Upper respiratory tract infection	3%	1%
Nasopharyngitis	3%	2%

Herpes zoster	3%	1%
Gastroenteritis	2%	2%

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

^b Rash events include dermatitis allergic, drug hypersensitivity, pruritus generalized, eosinophilic pustular folliculitis, rash, rash erythematous, rash generalized, rash macular, rash maculopapular, rash morbilliform, rash papular, rash pruritic, rash vesicular, and urticaria.

Laboratory Abnormalities: Table 3 provides a list of laboratory abnormalities (Grades 3–4) observed in Trial 903. With the exception of fasting cholesterol and fasting triglyceride elevations that were more common in the d4T group (40% and 9%) compared with the TDF group (19% and 1%) respectively, laboratory abnormalities observed in this trial occurred with similar frequency in the TDF and d4T treatment arms.

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

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

In ENCORE1 Trial, a summary of Grade 3 and 4 laboratory abnormalities is provided in Table 4.

Table 4 Grades 3-4 Laboratory Abnormalities in ≥ 2% in Either Treatment Group Through Week 48

Laboratory Parameter	EFV 400 mg + FTC + TDF	EFV 600 mg + FTC + TDF
	N = 321	N = 309
ALT	5%	3%
AST	2%	2%
Total bilirubin	0.3%	3%
Cholesterol	2%	5%
Neutrophils	2%	3%
Phosphorus	2%	3%

Pancreatitis: Pancreatitis, which has been fatal in some cases, has been observed in antiretroviral nucleoside-experienced pediatric subjects receiving 3TC alone or in combination with other antiretroviral agents [see *Warnings and Precautions (5.10)*].

Changes in Bone Mineral Density:

In HIV-1 infected adult subjects in Trial 903, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in subjects receiving TDF + 3TC + EFV (-2.2% ± 3.9) compared with subjects receiving d4T + 3TC + EFV (-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 TDF group vs. -2.4% ± 4.5 in the d4T 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 TDF-treated subjects vs. 21% of the d4T-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 TDF group and 6 subjects in the d4T 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 TDF group relative to the d4T group; however, except for bone-specific alkaline phosphatase, these changes resulted in values that remained within the normal range [see *Warnings and Precautions (5.13)*].

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of EFV, 3TC, or TDF. Because these reactions are

reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

EFV

Body as a Whole: allergic reactions, asthenia, redistribution/accumulation of body fat

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, emotionallability, mania, neurosis, paranoia, psychosis, suicide, catatonia

Respiratory: dyspnea

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

Special Senses: abnormal vision, tinnitus

3TC

Body as a Whole: redistribution/accumulation of body fat

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 [see *Warnings and Precautions (5.15)*], posttreatment exacerbation of hepatitis B [see *Warnings and Precautions (5.1)*].

Hypersensitivity: anaphylaxis, urticaria.

Musculoskeletal: muscle weakness, CPK elevation, rhabdomyolysis.

Skin: alopecia, pruritus.

TDF

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: 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

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 is a complete regimen for the treatment of HIV-1 infection; therefore, it 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 EFV and drugs that prolong the QTc interval. QTc prolongation has been observed with the use of EFV [see *Clinical Pharmacology (12.2)*]. Consider alternatives to EFV when coadministered with a drug with a known risk of Torsade de Pointes.

7.3 Drugs Affecting Renal Function

Tenofovir is primarily eliminated by the kidneys [see *Clinical Pharmacology (12.3)*]. Coadministration of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets with drugs that are eliminated by active tubular secretion may increase serum concentrations of tenofovir and/or coadministered drug. Some examples include, but are not limited to, acyclovir, cidofovir, ganciclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs [see *Warnings and Precautions (5.3)*]. Drugs that decrease renal function may increase concentrations of tenofovir.

Do not administer efavirenz, lamivudine, and tenofovir disoproxil fumarate tablets with HEPSERA (adefovir dipivoxil).

7.4 Cannabinoid Test Interaction

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

7.5 Established and Other Potentially Significant Drug Interactions

EFV 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 EFV.

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

No drug interaction studies have been conducted using efavirenz, lamivudine, and tenofovir disoproxil fumarate tablets. However, drug interaction studies have been conducted with the individual components of efavirenz, lamivudine, and tenofovir disoproxil fumarate tablets (EFV, 3TC, and TDF) [see *Clinical Pharmacology (12.3)*].

Drug interactions with EFV are summarized in Table 5. For pharmacokinetics data, [see *Clinical Pharmacology (12.3)*] Tables 7 and 8. This table includes potentially significant interactions, but is not all inclusive.

Table 5 Established and Other Potentially Significant Drug Interactions with EFV: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect	Clinical Comment
Anticoagulant: Warfarin	↑ or ↓ warfarin	Monitor INR and adjust warfarin dosage if necessary.
Anticonvulsants: Carbamazepine	↓ carbamazepine* ↓ EFV*	There are insufficient data to make a dose recommendation for EFV. Alternative anticonvulsant treatment should be used.
Phenytoin Phenobarbital	↓ anticonvulsant ↓ EFV	Monitor anticonvulsant plasma levels periodically because of potential for reduction in anticonvulsant and/or EFV plasma levels.
Antidepressants: Bupropion	↓ bupropion*	Increases in bupropion dosage should be guided by clinical response. Bupropion dose should not exceed the maximum recommended dose.
Sertraline	↓ sertraline*	Increases in sertraline dosage should be guided by clinical response.
Antifungals: Itraconazole Ketoconazole Posaconazole	↓ itraconazole* ↓ hydroxyitraconazole* ↓ ketoconazole ↓ posaconazole*	Consider alternative antifungal treatment because no dose recommendation for itraconazole or ketoconazole can be made. Avoid concomitant use unless the benefit outweighs the risks.
Anti-infective: Clarithromycin	↓ clarithromycin* ↑ 14-OH metabolite*	Consider alternatives to macrolide antibiotics because of the risk of QT interval prolongation.
Antimycobacterial: Rifabutin Rifampin	↓ rifabutin* ↓ EFV*	Increase daily dose of rifabutin by 50%. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week. Increase EFV total daily dose to 800 mg once daily when coadministered with rifampin to patients weighing 50 kg or more.
Antimalarials: Artemether/lumefantrine Atovaquone/ proguanil	↓ artemether* ↓ dihydroartemisinin* ↓ lumefantrine* ↓ atovaquone ↓ proguanil	Consider alternatives to artemether/lumefantrine because of the risk of QT interval prolongation [<i>see Warnings and Precautions (5.2)</i>]. Concomitant administration is not recommended.
Calcium channel blockers: Diltiazem Others (e.g., felodipine, nifedipine, verapamil)	↓ diltiazem* ↓ desacetyl diltiazem* ↓ N-monodesmethyldiltiazem* ↓ calcium channel blocker	Diltiazem dose adjustments should be guided by clinical response (refer to the full prescribing information for diltiazem). When coadministered with EFV, dosage adjustment of calcium channels blocker may be needed and should be guided by clinical response (refer to the full prescribing information for the calcium channel blocker).
HMG-CoA reductase inhibitors: Atorvastatin	↓ atorvastatin*	

Pravastatin Simvastatin	↓ pravastatin* ↓ simvastatin*	Plasma concentrations of atorvastatin, pravastatin, and simvastatin decreased. Consult the full prescribing information for the HMG-CoA reductase inhibitor for guidance on individualizing the dose.
Hepatitis C antiviral agents: Boceprevir	↓ boceprevir*	Concomitant administration of boceprevir is not recommended.
Elbasvir/Grazoprevir	↓ elbasvir ↓ grazoprevir	Coadministration of EFV with elbasvir/grazoprevir is contraindicated [<i>see Contraindications (4)</i>] because it may lead to loss of virologic response to elbasvir/grazoprevir.
Pibrentasvir/Glecaprevir	↓ pibrentasvir ↓ glecaprevir	Coadministration of EFV is not recommended because it may lead to reduced therapeutic effect of pibrentasvir/glecaprevir.
Simeprevir	↓ simeprevir* ↔ EFV	Concomitant administration of simeprevir is not recommended.
Velpatasvir/Sofosbuvir	↓ velpatasvir	Coadministration of EFV 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 EFV and sofosbuvir/velpatasvir/voxilaprevir is not recommended because it may result in loss of therapeutic effect of sofosbuvir/velpatasvir/voxilaprevir. Monitor for adverse reactions associated with TDF.
Ledipasvir/Sofosbuvir	↑ TDF	
Hepatitis B antiviral agents Adefovir dipivoxil		Concomitant administration of adefovir dipivoxil is not recommended.
Hormonal contraceptives: Oral Ethinyl estradiol/ Norgestimate		A reliable method of barrier contraception should be used in addition to hormonal contraceptives.
Implant Etonogestrel	↓ active metabolites of norgestimate* ↓ etonogestrel	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 EFV-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 EFV.
Narcotic analgesic: Methadone	↓ methadone*	

		Monitor for signs of methadone withdrawal and increase methadone dose if required to alleviate withdrawal symptoms.
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* The interaction between EFV 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 is administered with the following: aluminum/magnesium hydroxide antacids, azithromycin, cetirizine, famotidine, fluconazole, and lorazepam.

7.7 Drugs Inhibiting Organic Cation Transporters

3TC, a component of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, 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 3TC.

7.8 Sorbitol

Coadministration of single doses of 3TC and sorbitol resulted in a sorbitol dose-dependent reduction in 3TC. When possible, avoid use of sorbitol-containing medicines with 3TC [*see Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to efavirenz, lamivudine and tenofovir disoproxil fumarate tablets during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

There are retrospective case reports of neural tube defects in infants whose mothers were exposed to EFV-containing regimens in the first trimester of pregnancy.

Although a causal relationship has not been established between exposure to EFV 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, EFV should not be used in the first trimester of pregnancy. Advise pregnant women of the potential risk to a fetus.

Prospective pregnancy data from the APR are not sufficient to adequately assess this risk of birth defects or miscarriage. EFV and 3TC have been evaluated in a limited number of women as reported to the APR. Available data from the APR show no difference in the risk of major birth defects for EFV and 3TC 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) (*see Data*).

Oral administration of 3TC to pregnant rabbits during organogenesis resulted in embryoletality at systemic exposure (AUC) similar to the recommended clinical dose; however, no adverse development effects were observed with oral administration of 3TC to pregnant rats during organogenesis at plasma concentrations (C_{max}) 35 times the recommended clinical dose (*see Data*). No adverse developmental effects were observed when TDF was administered at doses/exposures ≥ 14 (TDF) and 2.7 (tenofovir) times those of the recommended daily dose of TDF (*see Data*).

The rate of miscarriage is not reported in the APR. The background risk for major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background rate for major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

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

Based on prospective reports from the APR of approximately 1000 live births following exposure to EFV-containing regimens (including over 800 live births exposed in the first trimester), there was no difference between EFV and overall birth defects compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. 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 EFV has also been prospectively reported. This case also included severe oblique facial clefts and amniotic banding, which have a known association with anophthalmia.

3TC: Based on prospective reports from the APR of over 11,000 exposures to 3TC during pregnancy resulting in live births (including over 4,500 exposed in the first trimester), there was no difference between 3TC and overall risk of birth defects for 3TC compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of defects in live births was 3.1% (95% CI: 2.6% to 3.6%) following first trimester exposure to 3TC-containing regimens and 2.8% (95% CI: 2.5%, 3.3%) following second/third trimester exposure to 3TC-containing regimens.

3TC pharmacokinetics were studied in pregnant women during 2 clinical studies conducted in South Africa. The trials assessed pharmacokinetics in 16 women at 36 weeks gestation using 150 mg 3TC twice daily with zidovudine, 10 women at 38 weeks gestation using 150 mg 3TC twice daily with zidovudine, and 10 women at 38 weeks gestation using 3TC 300 mg twice daily without other antiretrovirals. These trials were not designed or powered to provide efficacy information. 3TC 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 3TC crosses the placenta in humans. Based on limited data at delivery, median (range) amniotic fluid concentrations of 3TC were 3.9 (1.2 to 12.8)-fold greater compared with paired maternal serum concentration (n = 8).

TDF: Based on prospective reports from the APR exposures to TDF-containing regimens during pregnancy resulting in live births (including 3,342 exposed in the first trimester and 1,475 exposed in the second/third trimester), there was no increase in overall major birth defects with TDF compared with the background birth defect rate of 2.7% in a U.S. reference population of the MACDP. The prevalence of major birth defects in live births was 2.3% (95% CI: 1.8% to 2.8%) with first trimester exposure to TDF-containing regimens, and 2.1% (95% CI: 1.4% to 3.0%) with the second/third trimester exposure to TDF-containing regimens.

Prospective reports from the APR of overall major birth defects in pregnancies exposed to TDF are compared with a U.S. background major birth defect rate. Methodological limitations of the APR include the use of MACDP as the external comparator group. Limitations of using an external comparator include differences in methodology and populations, as well as confounding due to the underlying disease.

Animal Data: EFV: Effects of EFV on embryo-fetal development have been studied in three nonclinical species (cynomolgus monkeys, rats, and rabbits). In monkeys, EFV 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, EFV 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, EFV 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.

3TC: 3TC was administered orally to pregnant rats (at 90, 600, and 4,000 mg per kg per day) and rabbits (at 90, 300, and 1,000 mg per kg per day and at 15, 40, and 90 mg per kg per day) during organogenesis (on gestation Days 7 through 16 [rat] and 8 through 20 [rabbit]). No evidence of fetal malformations due to 3TC was observed in rats and rabbits at doses producing plasma concentrations (C_{max}) approximately 35 times higher than human exposure at the recommended daily dose. Evidence of early embryolethality was seen in the rabbit at system exposures (AUC) similar to those observed in humans, but there was no indication of this effect in the rat at

Table 7 Effect of EFV on Coadministered Drug Plasma C_{max}, AUC, and C_{min}

			Number of Subjects	Coadministered Drug (mean % change)		
Coadministered Drug	Dose	EFV Dose		C _{max} (90% CI)	AUC (90% CI)	C _{min} (90% CI)
Clarithromycin 14-OH metabolite	500 mg q12h x 7 days	400 mg qd x 7 days	11	↓ 26% (15-35%)	↓ 39% (30-46%)	↓ 53% (42-63%)
				↑ 49% (32-69%)	↑ 34% (18-53%)	↑ 26% (9-45%)
Fluconazole	200 mg x 7 days	400 mg qd x 7 days	10	↔	↔	↔
Itraconazole	200 mg q12h x 28 days	600 mg qd x 14 days	18	↓ 37% (20-51%)	↓ 39% (21-53%)	↓ 44% (27-58%)
Hydroxy-itraconazole				↓ 35% (12-52%)	↓ 37% (14-55%)	↓ 43% (18-60%)
Posaconazole	400 mg (oral suspension) bid x 10 and 20 days	400 mg qd x 10 and 20 days	11	↓ 45% (34-53%)	↓ 50% (40-57%)	NA
Rifabutin	300 mg qd x 14 days	600 mg qd x 14 days	9	↓ 32% (15-46%)	↓ 38% (28-47%)	↓ 45% (31-56%)
Voriconazole	400 mg po q12h x 1 day, then 200 mg po q12h x 8 days	400 mg qd x 9 days	NA	↓ 61% ^a	↓ 77% ^a	NA
	300 mg po q12h days 2-7	300 mg qd x 7 days	NA	↓ 36% ^b (21-49%)	↓ 55% ^b (45-62%)	NA
	400 mg po q12h days 2-7	300 mg qd x 7 days	NA	↑ 23% ^b (↓ 1-↑ 53%)	↓ 7% ^b (↓ 23-↑ 13%)	NA
Artemether/ lumefantrine	Artemether 20 mg/ lumefantrine 120 mg tablets (6 4-tablet doses over 3 days)	600 mg qd x 26 days	12			
Artemether				↓ 21%	↓ 51%	NA
dihydroartemisini n				↓ 38%	↓ 46%	NA
lumefantrine				↔	↓ 21%	NA
Atorvastatin	10 mg qd x 4 days	600 mg qd x 15 days	14	↓ 14% (1-26%)	↓ 43% (34-50%)	↓ 69% (49-81%)
Total active (including metabolites)				↓ 15% (2-26%)	↓ 32% (21-41%)	↓ 48% (23-64%)
Pravastatin	40 mg qd x 4 days	600 mg qd x 15 days	13	↓ 32% (↓ 59-↑ 12%)	↓ 44% (26-57%)	↓ 19% (0-35%)
Simvastatin	40 mg qd x 4 days	600 mg qd x 15 days	14	↓ 72% (63-79%)	↓ 68% (62-73%)	↓ 45% (20-62%)
Total active (including metabolites)				↓ 68% (55-78%)	↓ 60% (52-68%)	NA ^c
Carbamazepine	200 mg qd x 3 days, 200 mg bid x 3 days, then 400 mg qd x 29 days	600 mg qd x 14 days	12	↓ 20% (15-24%)	↓ 27% (20-33%)	↓ 35% (24-44%)
Epoxide metabolite				↔	↔	↓ 13% (↓ 30-↑ 7%)
Cetirizine	10 mg single dose	600 mg qd x 10 days	11	↓ 24% (18-30%)	↔	NA

Table 7 Effect of EFV on Coadministered Drug Plasma C_{max}, AUC, and C_{min}

Coadministered Drug	Dose	EFV Dose	Number of Subjects	Coadministered Drug (mean % change)		
				C _{max} (90% CI)	AUC (90% CI)	C _{min} (90% CI)
Diltiazem	240 mg x 21 days	600 mg qd x 14 days	13	↓ 60% (50-68%)	↓ 69% (55-79%)	↓ 63% (44-75%)
Desacetyl diltiazem				↓ 64% (57-69%)	↓ 75% (59-84%)	↓ 62% (44-75%)
N-monodes-methyl diltiazem				↓ 28% (7-44%)	↓ 37% (17-52%)	↓ 37% (17-52%)
Ethinyl estradiol/ Norgestimate	0.035 mg/0.25 mg x 14 days	600 mg qd x 14 days				
Ethinyl estradiol			21	↔	↔	↔
Norelgestromine			21	↓ 46% (39-52%)	↓ 64% (62-67%)	↓ 82% (79-85%)
Levonorgestrel			6	↓ 80% (77-83%)	↓ 83% (79-87%)	↓ 86% (80-90%)
Lorazepam	2 mg single dose	600 mg qd x 10 days	12	↑ 16% (2-32%)	↔	NA
Methadone	Stable maintenance 35-100 mg daily	600 mg qd x 14-21 days	11	↓ 45% (25-59%)	↓ 52% (33-66%)	NA
Bupropion	150 mg single dose (sustained-release)	600 mg qd x 14 days	13	↓ 34% (21-47%)	↓ 55% (48-62%)	NA
Hydroxy-bupropion				↑ 50% (20-80%)	↔	NA
Paroxetine	20 mg qd x 14 days	600 mg qd x 14 days	16	↔	↔	↔
Sertraline	50 mg qd x 14 days	600 mg qd x 14 days	13	↓ 29% (15-40%)	↓ 39% (27-50%)	↓ 46% (31-58%)

↑ 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 voriconazole (400 mg for 1 day, then 200 mg po q12h for 2 days).

^c Not available because of insufficient data.

^d Study conducted with ATRIPLA[®] coadministered with HARVONI[®].

^e The predominant circulating nucleoside metabolite of sofosbuvir.

^f Study conducted with ATRIPLA coadministered with SOVALDI[®] (sofosbuvir).

^g Study conducted with ATRIPLA coadministered with EPCLUSA[®].

NA = not available.

Table 8 Effect of Coadministered Drug on EFV Plasma C_{max}, AUC, and C_{min}

Coadministered Drug	Dose	EFV Dose	Number of Subjects	EFV (mean % change)		
				C _{max} (90% CI)	AUC (90% CI)	C _{min} (90% CI)
Boceprevir	800 mg tid x 6 days	600 mg qd x 16 days	NA	↑ 11% (2-20%)	↑ 20% (15-26%)	NA
Simeprevir	150 mg qd x 14 days	600 mg qd x 14 days	23	↔	↓ 10% (5-15%)	↓ 13% (7-19%)
Azithromycin	600 mg single dose	400 mg qd x 7 days	14	↔	↔	↔
Clarithromycin	500 mg q12h x 7 days	400 mg qd x 7 days	12	↑ 11% (3-19%)	↔	↔
Fluconazole	200 mg x 7 days	400 mg qd x 7 days	10	↔	↑ 16% (6-26%)	↑ 22% (5-41%)
Itraconazole	200 mg q12h	600 mg qd x	16	↔	↔	↔

Table 8 Effect of Coadministered Drug on EFV Plasma C_{max}, AUC, and C_{min}

Coadministered Drug	Dose	EFV Dose	Number of Subjects	EFV (mean % change)		
				C _{max} (90% CI)	AUC (90% CI)	C _{min} (90% CI)
	x 14 days	28 days				
Rifabutin	300 mg qd x 14 days	600 mg qd x 14 days	11	↔	↔	↓ 12% (↓ 24-↑ 1%)
Rifampin	600 mg x 7 days	600 mg qd x 7 days	12	↓ 20% (11-28%)	↓ 26% (15-36%)	↓ 32% (15-46%)
Voriconazole	400 mg po q12h x 1 day, then 200 mg po q12h x 8 days	400 mg qd x 9 days	NA	↑ 38% ^a	↑ 44% ^a	NA
	300 mg po q12h days 2-7	300 mg qd x 7 days	NA	↓ 14% ^b (7-21%)	↔ ^b	NA
	400 mg po q12h days 2-7	300 mg qd x 7 days	NA	↔ ^b	↑ 17% ^b (6-29%)	NA
Artemether/ Lumefantrine	Artemether 20 mg/ lumefantrine 120 mg tablets (6 4- tablet doses over 3 days)	600 mg qd x 26 days	12	↔	↓ 17%	NA
Atorvastatin	10 mg qd x 4 days	600 mg qd x 15 days	14	↔	↔	↔
Pravastatin	40 mg qd x 4 days	600 mg qd x 15 days	11	↔	↔	↔
Simvastatin	40 mg qd x 4 days	600 mg qd x 15 days	14	↓ 12% (↓ 28-↑ 8%)	↔	↓ 12% (↓ 25-↑ 3%)
Aluminum hydroxide 400 mg, magnesium hydroxide 400 mg, plus simethicone 40 mg	30 mL single dose	400 mg single dose	17	↔	↔	NA
Carbamazepine	200 mg qd x 3 days, 200 mg bid x 3 days, then 400 mg qd x 15 days	600 mg qd x 35 days	14	↓ 21% (15-26%)	↓ 36% (32-40%)	↓ 47% (41-53%)
Cetirizine	10 mg single dose	600 mg qd x 10 days	11	↔	↔	↔
Diltiazem	240 mg x 14 days	600 mg qd x 28 days	12	↑ 16% (6-26%)	↑ 11% (5-18%)	↑ 13% (1-26%)
Famotidine	40 mg single dose	400 mg single dose	17	↔	↔	NA
Paroxetine	20 mg qd x 14 days	600 mg qd x 14 days	12	↔	↔	↔
Sertraline	50 mg qd x 14 days	600 mg qd x 14 days	13	↑ 11% (6-16%)	↔	↔

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

^a 90% CI not available.

^b Relative to steady-state administration of efavirenz (600 mg once daily for 9 days).

NA = not available.

3TC

Effect of 3TC on the Pharmacokinetics of Other Agents: Based on *in vitro* study results, 3TC 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 3TC: 3TC is a substrate of MATE1, MATE2-K, and OCT2 *in vitro*. Trimethoprim (an inhibitor of these drug transporters) has been shown to increase 3TC plasma concentrations. This interaction is not considered clinically significant as no dose adjustment of 3TC is needed.

3TC 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 3TC. Therefore, coadministration of drugs that are inhibitors of these efflux transporters is unlikely to affect the disposition and elimination of 3TC.

Interferon Alfa: There was no significant pharmacokinetic interaction between 3TC and interferon alfa in a trial of 19 healthy male subjects [see *Warnings and Precautions (5.9)*].

Ribavirin: *In vitro* data indicate ribavirin reduces phosphorylation of 3TC, 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 3TC (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 (5.9)*].

Sorbitol (Excipient): 3TC 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 3TC 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 3TC 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 C_{max} of 3TC, respectively.

Trimethoprim/Sulfamethoxazole: 3TC 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 3TC 300 mg with the fifth dose in a crossover design. Coadministration of TMP/SMX with 3TC 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 3TC renal clearance. The pharmacokinetic properties of TMP and SMX were not altered by coadministration with 3TC. There is no information regarding the effect on 3TC pharmacokinetics of higher doses of TMP/SMX such as those used in treat PCP.

TDF

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

Table 9 summarizes pharmacokinetic effects of coadministered drug on tenofovir pharmacokinetics. No clinically significant drug interactions have been observed between TDF and ribavirin or sofosbuvir.

Table 9 Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir^a in the Presence of the Coadministered Drug

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Tenofovir Pharmacokinetic Parameters ^b (90% CI)		
			C _{max}	AUC	C _{min}
Ledipasvir/ Sofosbuvir ^{e,f}	90/400 once daily × 10days	24	↑47 (↑37to↑58)	↑35 (↑29to↑42)	↑47 (↑38to↑57)
Ledipasvir/ Sofosbuvir ^{e,g}		23	↑64 (↑54to↑74)	↑50 (↑42to↑59)	↑59 (↑49to↑70)
Ledipasvir/ Sofosbuvir ^h	90/400 once daily × 14days	15	↑79 (↑56to↑104)	↑98 (↑77to↑123)	↑163 (↑132to↑197)
Sofosbuvir ⁱ	400 single dose	16	↑25	↔	↔

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Tenofovir Pharmacokinetic Parameters ^b (90% CI)		
			C _{max}	AUC	C _{min}
			(↑8to ↑45)		
Sofosbuvir/ Velpatasvir ^j	400/100 once daily	24	↑44 (↑33to↑55)	↑40 (↑34to↑46)	↑84 (↑76to↑92)
Sofosbuvir/ Velpatasvir ^k	400/100 once daily	30	↑46 (↑39to↑54)	↑40 (↑34to↑45)	↑70 (↑61to↑79)
Sofosbuvir/ Velpatasvir/ Voxilaprevir ^l	400/100/100 + Voxilaprevir ^m 100 once daily	29	↑48 (↑36 to ↑61)	↑39 (↑32 to ↑46)	↑47 (↑38 to ↑56)
Tacrolimus	0.05 mg/kg twice daily × 7 days	21	↑13 (↑1to↑27)	↔	↔

^a Subjects received VIREAD 300 mg once daily.

^b Increase = ↑; Decrease = ↓; No Effect = ↔; NC = Not Calculated

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

^f Comparison based on exposures when administered as atazanavir/ritonavir + FTC/TDF.

^g Comparison based on exposures when administered as darunavir/ritonavir + FTC/TDF.

^h Study conducted with ATRIPLA (EFV/FTC/TDF) coadministered with HARVONI; coadministration with HARVONI also results in comparable increases in tenofovir exposure when TDF is administered as COMPLERA (FTC/rilpivirine/TDF), or TRUVADA + dolutegravir.

ⁱ Study conducted with ATRIPLA coadministered with SOVALDI (sofosbuvir).

^j Study conducted with COMPLERA coadministered with EPCLUSA; coadministration with EPCLUSA also results in comparable increases in tenofovir exposures when TDF is administered as ATRIPLA, STRIBILD (elvitegravir/cobicistat/FTC/TDF), TRUVADA + atazanavir/ritonavir, or TRUVADA + darunavir/ritonavir.

^k Administered as raltegravir + FTC/TDF.

^l Comparison based on exposures when administered as darunavir/ritonavir + FTC/TDF.

^m Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

12.4 Microbiology

Mechanism of Action

EFV: EFV is an NNRTI of HIV-1. EFV activity is mediated predominantly by noncompetitive inhibition of HIV-1 reverse transcriptase (RT). HIV-2 RT and human cellular DNA polymerases α , β , γ , and δ are not inhibited by EFV.

3TC: 3TC is a synthetic nucleoside analogue. Intracellularly, 3TC 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.

TDF: TDF is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. TDF requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate, an obligate chain terminator. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase 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 in Cell Culture

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

3TC: The antiviral activity of 3TC against HIV-1 was assessed in a number of cell lines including monocytes and PBMCs using standard susceptibility assays. EC₅₀ values were in the range of 0.003 to 15 microM (1 microM = 0.23 mcg per mL). The median EC₅₀ 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 EC₅₀ values against HIV-2 isolates (n = 4) ranged from 0.003 to 0.120 microM in PBMCs. 3TC 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.

TDF: 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 EC₅₀ (50% effective concentration) values for tenofovir were in the range of 0.04 microM to 8.5 microM. Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC₅₀ values ranged from 0.5 µM to 2.2 µM) and strain-specific activity against HIV-2 (EC₅₀ values ranged from 1.6 µM to 5.5 µM). Please see the full prescribing information for TDF for information regarding the inhibitory activity of TDF against HBV.

Resistance in Cell Culture

EFV: In cell culture, HIV-1 isolates with reduced susceptibility to EFV (>380-fold increase in EC₉₀ value) emerged rapidly in the presence of drug. Genotypic characterization of these viruses identified single amino acid substitutions L100I or V179D, double substitutions L100I/V108I, and triple substitutions L100I/V179D/Y181C in RT.

Clinical isolates with reduced susceptibility in cell culture to EFV 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 EFV in combination with indinavir, or with 3TC plus zidovudine. The K103N substitution was the most frequently observed.

3TC: 3TC-resistant variants of HIV-1 have been selected in cell culture. Genotypic analysis showed that the resistance was predominantly due to a methionine to valine or isoleucine (M184V/I).

TDF: 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 TDF regimen.

Cross-Resistance

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

3TC: Cross-resistance among certain NRTIs has been observed. 3TC-resistant HIV-1 isolates were cross-resistant in cell culture to didanosine (ddI). Cross-resistance is also expected with abacavir and emtricitabine as these select M184V substitutions.

TDF: Cross-resistance among certain NRTIs has been recognized. The K65R and K70E substitution selected by tenofovir are also selected in some HIV-1 infected subjects treated with abacavir, didanosine, or zalcitabine. HIV-1 isolates with the K65R substitution also showed reduced susceptibility to emtricitabine and 3TC. 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 TDF. 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

EFV: Long-term carcinogenicity studies in mice and rats were carried out with EFV. Mice were dosed with 0, 25, 75, 150, or 300 mg/kg/day for 2 years. Incidences of hepatocellular adenomas and carcinomas and pulmonary alveolar/bronchiolar adenomas 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.

EFV 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.

EFV did not impair mating or fertility of male or female rats, and did not affect sperm of treated male rats. The reproductive performance of offspring born to female rats given EFV was not affected. 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

3TC: Long-term carcinogenicity studies with 3TC 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.

3TC was mutagenic in an L5178Y mouse lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes. 3TC 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 an assay for unscheduled DNA synthesis in rat liver. 3TC showed no evidence of *in vivo* genotoxic activity in the rat at oral doses of up to 2,000 mg per kg, producing plasma levels of 35 to 45 times those in humans at the recommended dose for HIV-1 infection.

TDF: Long-term oral carcinogenicity studies of TDF 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.

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

There were no effects on fertility, mating performance or early embryonic development when TDF 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

EFV: Nonsustained convulsions were observed in 6 of 20 monkeys receiving EFV at doses yielding plasma AUC values 4- to 13-fold greater than those in humans given the recommended dose [see *Warnings and Precautions (5.11)*].

TDF: Tenofovir and TDF 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

The efficacy of EFV 400 mg, 3TC 300 mg, and TDF 300 mg in the treatment of HIV-1 infection in adults with no antiretroviral treatment history was established in trials of:

- Trial 903 which evaluated the efficacy of a three-drug regimen including EFV 600 mg, 3TC 300 mg and TDF 300 mg
- ENCORE1, which evaluated the comparability of 400 mg of EFV in a triple drug regimen to a 600 mg dose of EFV in a triple drug regimen.

Trial 903: Data through 144 weeks are reported for Trial 903, a double-blind, active-controlled multicenter trial comparing TDF (300 mg once daily) administered in combination with 3TC and EFV versus stavudine (d4T), 3TC, and EFV 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. Table 10 provides treatment outcomes through 48 and 144 weeks.

Table 10 Outcomes of Randomized Treatment at Week 48 and 144 (Trial 903)

Outcomes	At Week 48		At Week 144	
	TDF+3TC +EFV (N=299)	d4T+3TC +EFV (N=301)	TDF+3TC+EFV (N=299)	d4T+3TC+EFV (N=301)
Responder ^a	79%	82%	68%	62%
Virologic failure ^b	6%	4%	10%	8%
Rebound	5%	3%	8%	7%
Never suppressed	0%	1%	0%	0%
Added an antiretroviral agent	1%	1%	2%	1%
Death	<1%	1%	<1%	2%
Discontinued due to adverse event	6%	6%	8%	13%
Discontinued for other reasons ^c	8%	7%	14%	15%

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

b. Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Week 48 and 144.

c. Includes lost to follow-up, subject's withdrawal, noncompliance, protocol violation and other reasons.

Achievement of plasma HIV-1 RNA concentrations of less than 400 copies/mL at Week 144 was similar between the two treatment groups for the population stratified at baseline on the basis of HIV-1 RNA concentration (> or ≤100,000 copies/mL) and CD4⁺ cell count (< or ≥200 cells/mm³). Through 144 weeks of therapy, 62% and 58% of subjects in the TDF and d4T 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 TDF arm and 283 cells/mm³for the d4T arm. Through 144 weeks, 11 subjects in the TDF group and 9 subjects in the d4T group experienced a new CDC Class C event.

The ENCORE1 Trial was a randomized, multinational clinical study comparing EFV 400 mg vs. EFV 600 mg in 630 antiretroviral-naïve adult subjects. Subjects were randomized 1:1 to receive EFV 400 mg in combination with TDF 300 mg plus FTC 200 mg all given once daily or EFV 600 mg in combination with TDF 300 mg/FTC 200 mg given once daily. The randomization was stratified by the clinical sites and the screening visit plasma HIV RNA level, either < 100,000 copies/mL or ≥ 100,000 copies/mL.

Subjects had a mean age of 36 years (range 18 to 69), 68% were male, 37% were of African heritage, 33% were of Asian ethnicity, 17% were Hispanic and 13% were Caucasian.

The mean baseline CD4⁺ cell count was 273 cells/mm³ (range 38 to 679). Median baseline viral load was 56,469 copies/mL (range 162 to 10,000,000). Thirty-four percent of subjects had baseline viral load of ≥ 100,000 copies/mL.

Table 11 provides treatment outcomes through Week 48.

Table 11 Virologic Outcomes of Randomized Treatment in Trial ENCORE1 in Treatment-Naïve Subjects at Week 48

Outcomes (< 50 copies/mL)	At Week 48	
	EFV400 mg +FTC+ TDF (N = 321)	EFV600 mg +FTC + TDF (N = 309)
Responder^a HIV-1 RNA < 50 copies/mL	86%	84%
Virologic failure ^b HIV-1 RNA ≥ 50 copies/mL	11%	11%
Rebound	9%	8%
Never suppressed	2%	3%
Death	1%	1%
Discontinued for other reasons ^c	2%	4%

a. Subjects achieved confirmed HIV-1 RNA < 50 copies/mL at Week 48.

b. Includes confirmed viral rebound and failure to achieve confirmed < 50 copies/mL through Week 48

^c Includes discontinued due to Adverse Event, lost to follow-up, subject's withdrawal, noncompliance, protocol violation and other reasons.

Achievement of plasma HIV-1 RNA concentrations of less than 50 copies/mL at Week 48 was similar between the two treatment groups for the population stratified at baseline on the basis of HIV-1 RNA concentration (< or ≥100,000 copies/mL). The mean increase at Week 48 from baseline in CD4⁺cell count was 183 cells/mm³ for the EFV 400 mg arm and 158 cells/mm³ for the EFV 600 mg arm. Through 48 weeks, 11 subjects in the EFV 400 mg group and 5 subjects in the EFV 600 mg group experienced a new CDC Class C event.

16 HOW SUPPLIED/STORAGE AND HANDLING

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets 400mg/300mg/300mg are pink colored, capsule shaped, biconvex, film coated tablets debossed with "F 31" on one side and plain on the other side.

Bottle of 30 tablets with silica gel desiccant, induction seal, and child-resistant cap - NDC 33342-362-07

Bottle of 90 tablets with silica gel desiccant, induction seal, and child-resistant cap - NDC 33342-362-10

Bottle of 180 tablets with silica gel desiccant and induction seal - NDC 33342-362-57

Store below 30°C (86°F)

Store and dispense in original bottle, protect from moisture, and keep bottle tightly closed. Do not remove desiccant. Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Drug Interactions: Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets may interact with many drugs; therefore, advise patients to report to their healthcare provider the use of any other prescription, nonprescription medication, or herbal products, particularly St. John's wort [*see Contraindications (4) and Drug Interactions (7)*].

Patients with Hepatitis B or C Co-infection: Inform patients that severe acute exacerbations of hepatitis B have been reported in patients infected with hepatitis B virus (HBV) who have discontinued TDF and 3TC, two components of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. Advise patients not to discontinue efavirenz, lamivudine and tenofovir disoproxil fumarate tablets without first informing their healthcare provider. All patients should be tested for HBV infection before or when starting efavirenz, lamivudine and tenofovir disoproxil fumarate tablets and those who are infected with HBV need close medical follow-up for several months after stopping efavirenz, lamivudine and tenofovir disoproxil fumarate tablets to monitor for exacerbations of hepatitis [*see Warnings and Precautions (5.1)*].

Inform patients with HIV-1/HCV co-infection that hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin [*see Warnings and Precautions (5.9)*].

New Onset or Worsening Renal Impairment: Inform patients that renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported. Advise patients with creatinine clearance less than 50 mL per min or patients with end-stage renal disease (ESRD) requiring hemodialysis to avoid efavirenz, lamivudine and tenofovir disoproxil fumarate tablets with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple NSAIDs) [*see Dosage and Administration (2.3), Warnings and Precautions (5.3)*].

Psychiatric Symptoms: Inform patients that serious psychiatric symptoms including severe depression, suicide attempts, aggressive behavior, delusions, paranoia, psychosis-like symptoms and catatonia have been reported in patients receiving EFV [*see Warnings and Precautions (5.4)*]. Advise patients to seek immediate medical evaluation if they experience severe psychiatric adverse experiences. Advise patients to inform their physician of any history of mental illness or substance abuse.

Nervous System Symptoms: Inform patients 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 EFV, a component of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets [*see Warnings and Precautions (5.5)*]. Dosing at bedtime may improve the tolerability of these symptoms, which are likely to improve with continued therapy. Alert patients to the potential for additive effects when efavirenz, lamivudine and tenofovir disoproxil fumarate tablets is used concomitantly with alcohol or psychoactive drugs. Instruct patients that if they experience NSS to avoid potentially hazardous tasks such as driving or operating machinery [*see Dosage and Administration (2.2)*].

Embryo-Fetal Toxicity: Apprise patients of the potential harm to the fetus if efavirenz, lamivudine and tenofovir disoproxil fumarate tablets is used during the first trimester of pregnancy, or if the patient becomes pregnant while taking this drug. Instruct adults and adolescents of childbearing potential receiving efavirenz, lamivudine and tenofovir disoproxil fumarate tablets to avoid pregnancy and to notify their healthcare provider if they become pregnant or plan to become pregnant with taking efavirenz, lamivudine and tenofovir disoproxil fumarate tablets [see *Warnings and Precautions (5.6)*]. A reliable form of barrier contraception must always be used in combination with other methods of contraception, including oral or other hormonal contraception. Because of the long half-life of EFV, recommend use of adequate contraceptive measures for 12 weeks after discontinuation of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets [see *Use in Specific Populations (8.1, 8.3)*].

Rash: Inform patients that rash is a common side effect of EFV, a component of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets [see *Warnings and Precautions (5.7)*]. 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.

Hepatotoxicity: 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 healthcare provider promptly if such symptoms occur [see *Warnings and Precautions (5.8)*].

Risk of Pancreatitis: Advise parents or guardians to monitor pediatric patients for signs and symptoms of pancreatitis [see *Warnings and Precautions (5.10)*].

Convulsions: Inform patients that convulsions have been reported with the use of EFV, a component of a component of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. Patients who receiving concomitant anticonvulsant medications primarily metabolized by the liver may require monitoring of plasma levels [see *Warnings and Precautions (5.11)*].

Lipid Elevations: Advise patients treatment with EFV, a component of a component of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, has resulted in increases in the concentration of total cholesterol and triglycerides [see *Warnings and Precautions (5.12)*].

Bone Loss and Mineralization Defects: Inform patients that decreases in bone mineral density have been observed with the use of TDF, a component of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. Advise patients that bone mineral density monitoring may be performed in patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss [see *Warnings and Precautions (5.13)*].

Immune Reconstitution Syndrome: Advise patients to inform their healthcare provider immediately of any signs and symptoms of infection as inflammation from previous infection may occur soon after combination antiretroviral therapy, including when efavirenz, lamivudine, and tenofovir disoproxil fumarate tablets is started [see *Warnings and Precautions (5.14)*].

Lactic Acidosis/Hepatomegaly: Inform patients that lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should be suspended in any patients who develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity (including nausea, vomiting, unusual or unexpected stomach discomfort, and weakness) [see *Warnings and Precautions (5.15)*].

Pregnancy Exposure Registry: Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to efavirenz, lamivudine, and tenofovir disoproxil fumarate tablets during pregnancy [see *Use in Specific Populations (8.1)*].

Lactation: Instruct mothers with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in the breast milk [see *Use in Specific Populations (8.2)*].

Missed Dose: Instruct patients that if they miss a dose of efavirenz, lamivudine, and tenofovir disoproxil fumarate tablets, to take it as soon as they remember. Advise patients not to double their next dose or take more than the prescribed dose.

Storage: Instruct patients to store efavirenz, lamivudine, and tenofovir disoproxil fumarate tablets in the original bottle, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant.

Other brands listed are the registered trademarks of their respective owners and are not trademarks of Macleods Pharmaceuticals Limited.

Rx only

Manufactured for:

Macleods Pharma USA, Inc.

Plainsboro, NJ08536

Manufactured by:

Macleods Pharmaceuticals Ltd.

Daman (U.T.), INDIA

Patient Information

Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, 400 mg/300 mg/300 mg (EF-a-VIR-enz, la-MIV-ue-deen and ten-OF-oh-vir DYE-soe-PROX-il FUE-ma-rate)

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:

- **Worsening of hepatitis B virus (HBV) infection.** Your healthcare provider will test you for HBV before starting efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. If you have HBV infection and take efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, your HBV may get worse (flare-up) if you stop taking efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. A “flare-up” is when your HBV infection suddenly returns in a worse way than before.
 - Do not run out of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. Refill your prescription or talk to your healthcare provider before your efavirenz, lamivudine and tenofovir disoproxil fumarate tablets is all gone.
 - **Do not stop taking efavirenz, lamivudine and tenofovir disoproxil fumarate tablets without first talking with your healthcare provider.** If you stop taking efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, your healthcare provider will need to check your health often and do blood tests regularly for several months to check your liver.
- **Changes in the electrical activity of your heart called QT prolongation. QT prolongation can cause irregular heartbeats that can be life-threatening.** Tell your healthcare provider if you feel faint, lightheaded, dizzy, or feel your heart beating irregularly or fast during treatment with efavirenz, lamivudine and tenofovir disoproxil fumarate tablets.
- **New or worse kidney problems, including kidney failure.** Your healthcare provider will do blood and urine tests to check your kidneys before and during treatment with efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. Tell your healthcare provider if you get signs and symptoms of kidney problems, including bone pain that does not go away or worsening bone pain, pain in your arms, hands, legs or feet, broken (fractured) bones, muscle pain or weakness.
- **Serious mental health problems. Get medical help right away if you get any of the following symptoms:**
 - feel sad or hopeless
 - feel anxious or restless
 - do not trust other people
 - hear or see things that are not real
 - are not able to move or speak normally
 - 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

For more information about side effects, see “**What are the possible side effects of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets?**”

What is efavirenz, lamivudine and tenofovir disoproxil fumarate tablets?

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets is a prescription medicine that is used without other antiviral medicines to treat human immunodeficiency virus-1 (HIV-1) in adults and children who weigh at least 77 pounds (35 kg).

HIV-1 is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets contains the prescription medicines efavirenz, lamivudine and tenofovir disoproxil fumarate.

Do not take efavirenz, lamivudine and tenofovir disoproxil fumarate tablets if you:

- are allergic to efavirenz, lamivudine, tenofovir disoproxil fumarate, or any of the ingredients in efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. See the end of this Patient Information leaflet for a complete list of ingredients in efavirenz, lamivudine and tenofovir disoproxil fumarate tablets.
- are currently taking elbasvir and grazoprevir.

Before you take efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, tell your healthcare provider about all of your medical conditions, including if you:

- have liver problems, including hepatitis B or C infection
- have kidney problems, including end-stage renal disease (ESRD) that requires dialysis
- have a history of mental health problems
- have a history of drug or alcohol abuse
- have a heart problem, including QT prolongation
- have bone problems, including a history of bone fractures
- have a history of seizures
- are pregnant or plan to become pregnant. Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets may harm

your unborn baby.

- You should not become pregnant during treatment with efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with efavirenz, lamivudine and tenofovir disoproxil fumarate tablets.
- Females who are able to become pregnant should use effective birth control (contraception) during treatment with efavirenz, lamivudine and tenofovir disoproxil fumarate tablets and for 12 weeks after stopping treatment. A barrier form of birth control should always be used along with another type of birth control.
- Your healthcare provider should do a pregnancy test before you start efavirenz, lamivudine and tenofovir disoproxil fumarate tablets.

Pregnancy Registry. There is a pregnancy registry for women who take efavirenz, lamivudine and tenofovir disoproxil fumarate tablets during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry.

- are breastfeeding or plan to breastfeed. Do not breastfeed if you take efavirenz, lamivudine and tenofovir disoproxil fumarate tablets.
 - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 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 over-the-counter medicines, vitamins and herbal supplements.

Some medicines interact with efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. 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 works. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

- You can ask your healthcare provider or pharmacist for a list of medicines that interact with efavirenz, lamivudine and tenofovir disoproxil fumarate tablets.
- Do not start taking a new medicine without telling your healthcare provider. Your healthcare provider can tell you if it is safe to take efavirenz, lamivudine and tenofovir disoproxil fumarate tablets with other medicines.

How should I take efavirenz, lamivudine and tenofovir disoproxil fumarate tablets?

- Take efavirenz, lamivudine and tenofovir disoproxil fumarate tablets exactly as your healthcare provider tells you to take it.
- Take efavirenz, lamivudine and tenofovir disoproxil fumarate tablets 1 time each day, preferably at bedtime. Taking efavirenz, lamivudine and tenofovir disoproxil fumarate tablets at bedtime might help to make some of the side effects less bothersome.
- Take efavirenz, lamivudine and tenofovir disoproxil fumarate tablets 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. Do not double your dose or take more tablets than prescribed by your healthcare provider.
- Stay under the care of your healthcare provider during treatment with efavirenz, lamivudine and tenofovir disoproxil fumarate tablets.
- Do not run out of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. The virus in your blood may increase and the virus may become harder to treat. When your supply starts to run low, get more from your healthcare provider or pharmacy.
- If you take too much efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, go to the nearest hospital emergency room right away.

What should I avoid while taking efavirenz, lamivudine and tenofovir disoproxil fumarate tablets?

You should avoid taking medicines that contain sorbitol during treatment with efavirenz, lamivudine and tenofovir disoproxil fumarate tablets.

What are the possible side effects of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets?

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets may cause serious side effects, including:

- See **“What is the most important information I should know about efavirenz, lamivudine and tenofovir disoproxil fumarate tablets?”**
- **Nervous system problems** are common in people who take efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, but can be severe. These symptoms usually begin during the first or second day of treatment with efavirenz, lamivudine and tenofovir disoproxil fumarate tablets and usually go away after 2 to 4 weeks of treatment. These symptoms may become worse if you drink alcohol or take a medicine for mental health problems. Symptoms may include:
 - dizziness
 - trouble concentrating
 - trouble sleeping
 - drowsiness

- unusual dreams
- headache
- seeing or hearing things that are not real (hallucinations)

If you get symptoms of nervous system problems during treatment with efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, you should avoid driving, operating machinery, or doing anything that needs you to be alert.

- **Skin reactions and allergic reactions.** Skin reactions or rash can happen and can sometimes be severe. Skin rash usually goes away without any change in treatment. If you develop a rash or a rash with any of the following symptoms, call your healthcare provider right away:

- itching
- fever
- swelling of your face
- blisters or skin lesions
- peeling skin
- mouth sores
- red or inflamed eyes

- **Severe liver problems.** In some cases, severe liver problems can lead to death. Your liver may become large (hepatomegaly) and you may develop fat in your liver (steatosis). Inflammation of your liver (hepatitis) that can lead to liver failure requiring a liver transplant has been reported in some people treated with efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. Your healthcare provider may do blood tests to check your liver before and during treatment with efavirenz, lamivudine and tenofovir disoproxil fumarate tablets.

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

- your skin or the white part of your eyes turns yellow (jaundice)
- dark or “tea-colored” urine
- light-colored stools (bowel movements)
- confusion
- tiredness
- loss of appetite for several days or longer
- nausea and vomiting
- pain, aching, or tenderness on the right side of your stomach-area
- weakness
- stomach (abdomen) swelling

- **Use with interferon and ribavirin-based regimens.** Worsening of liver disease that has caused death has happened in people infected with HIV-1 and hepatitis C virus who were taking antiretroviral medicines for HIV-1 and were also being treated for hepatitis C with interferon alfa with or without ribavirin. If you are taking efavirenz, lamivudine and tenofovir disoproxil fumarate tablets and interferon alfa with or without ribavirin, tell your healthcare provider if you have any new symptoms.

- **Risk of inflammation of the pancreas (pancreatitis).** Children may be at risk for developing pancreatitis during treatment with efavirenz, lamivudine and tenofovir disoproxil fumarate tablets if they:

- have taken nucleoside analogue medicines in the past
- have a history of pancreatitis
- have other risk factors for pancreatitis

Call your healthcare provider right away if your child develops signs and symptoms of pancreatitis including severe upper stomach-area pain, with or without nausea and vomiting. Your healthcare provider may tell you to stop giving efavirenz, lamivudine and tenofovir disoproxil fumarate tablets to your child if their symptoms and blood test results show that your child may have pancreatitis.

- **Seizures.** Seizures are more likely to happen if you have had seizures in the past.
- **Increases in blood fat levels (cholesterol and triglycerides).** Your healthcare provider will check your blood fat levels before and during 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 tests to check your bones. Tell your healthcare provider if you have any bone pain, pain in your hands or feet, or muscle pain or weakness during treatment with efavirenz, lamivudine and tenofovir disoproxil fumarate tablets.
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV-1 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 healthcare provider if you start having new symptoms after starting your HIV-1 medicine.
- **Too much lactic acid in your blood (lactic acidosis).** Lactic acidosis is a serious medical emergency that can lead to death.

Tell your healthcare provider right away if you get any of the following symptoms that could be signs of lactic acidosis:

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

The most common side effects of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are rash and dizziness. 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. **Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.**

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

- Store efavirenz, lamivudine and tenofovir disoproxil fumarate tablets below 86°F (30°C).
- Keep efavirenz, lamivudine and tenofovir disoproxil fumarate tablets in the original container.
- Keep the bottle tightly closed. The bottle contains a desiccant that helps to keep the tablets dry. Do not remove desiccant.

Keep efavirenz, lamivudine and tenofovir disoproxil fumarate tablets and all medicines out of the reach of children.

General information about the safe and effective use of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use efavirenz, lamivudine and tenofovir disoproxil fumarate tablets for a condition for which it was not prescribed. Do not give efavirenz, lamivudine and tenofovir disoproxil fumarate tablets to other people, even if they have the same symptoms that you have. It may harm them. 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 ingredient: efavirenz, lamivudine, and tenofovir disoproxil fumarate

Inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch, poloxamer, and sodium lauryl sulphate. The tablets are coated with ferric oxide red, hydroxypropyl methylcellulose, lactose monohydrate, titanium dioxide, and triacetin.

Manufactured for: **Macleods Pharma USA, Inc.**, Plainsboro, NJ 08536
Manufactured by: **Macleods Pharmaceuticals Ltd.**, Daman (U.T.), INDIA
For more information, call Macleods Pharma USA, Inc. at 1-888-943-3210.

This Patient Information has been approved by the U.S. Food and Drug Administration.

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