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: 2018

WARNING: POST TREATMENT ACUTE EXACERBATIONS OF HEPATITIS B

See full prescribing information for complete boxed warning.

- **Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with HBV and human immunodeficiency virus (HIV-1) and have discontinued lamivudine and tenofovir disoproxil fumarate. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.1)**

----------RECENT MAJOR CHANGES----------

Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.6, 5.13, 5.14)	10/2019
Warnings and Precautions, Use with Interferon-and Ribavirin-Based Regimens (previous 5.10)	Removed 10/2019

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

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are three-drug combination of efavirenz (EFV), a non-nucleoside reverse transcriptase inhibitor, and lamivudine (3TC) and tenofovir disoproxil fumarate (TDF), both nucleo(t)side reverse transcriptase inhibitors and are indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adult and pediatric patients weighing at least 40 kg. (1)

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

- Testing: Prior to initiation and during treatment with efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, patients should be tested for hepatitis B virus infection, and estimated creatinine clearance, urine glucose, and urine protein should be obtained. (2.1)
- Recommended dose: One tablet taken orally once daily 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: 600 mg efavirenz, 300 mg lamivudine and 300 mg tenofovir disoproxil fumarate (equivalent to 245 mg of tenofovir disoproxil). (3)

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

- Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are contraindicated in patients with previous hypersensitivity (e.g., Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the components of this product. (4)
- Coadministration with elbasvir/grazoprevir. (4)

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

- Lactic Acidosis/Severe Hepatomegaly with Steatosis: Discontinue treatment in patients who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity. (5.2)
- New Onset or Worsening Renal Impairment: Can include acute renal failure and Fanconi syndrome. Avoid administering efavirenz, lamivudine and tenofovir disoproxil fumarate tablets with concurrent or recent use of nephrotoxic drugs.(5.4)
- Serious Psychiatric Symptoms: Immediate medical evaluation is recommended for serious psychiatric symptoms such as severe depression or suicidal ideation. (5.5)
- 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. (5.6)
- Rash: Rash usually begins within 1 to 2 weeks after initiating therapy and resolves within 4 weeks. Discontinue if severe rash develops. (5.8)
- 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. (5.9, 8.7)
- Pancreatitis: Use with caution in pediatric patients with a history of pancreatitis or other significant risk factors for pancreatitis. Discontinue efavirenz, lamivudine and tenofovir disoproxil fumarate as clinically appropriate. (5.10)
- 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): Observed in HIV-infected patients. Consider assessment of BMD in patients with a history of pathologic fracture or other risk factors for osteoporosis or bone loss. (5.13)
- Immune Reconstitution Syndrome: Observed in HIV-infected patients. May necessitate further evaluation and treatment. (5.14)
- Redistribution/Accumulation of Body Fat: Observed in HIV-infected patients receiving antiretroviral combination therapy. (5.15)

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

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

To report SUSPECTED ADVERSE REACTIONS, contact Laurus Generics Inc. at 1-833-3-LAURUS (1-833-352-8787) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Efavirenz, lamivudine and tenofovir disoproxil fumarate 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 can alter the concentrations of other drugs and other drugs may alter the concentration of efavirenz, lamivudine and tenofovir disoproxil fumarate. The potential for drug-drug interactions should be considered before and during therapy. (5.3, 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. (5.7, 8.1, 8.3)
- 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.

Revised: 11/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: POST TREATMENT ACUTE EXACERBATIONS OF HEPATITIS B

Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine or tenofovir disoproxil fumarate, two components of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment ***[see Warnings and Precautions (5.1)].***

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

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

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

It is recommended that serum creatinine, serum phosphorus, estimated creatinine clearance, urine glucose, and urine protein be assessed before initiating efavirenz, lamivudine and tenofovir disoproxil fumarate tablets and during therapy in all patients as clinically appropriate *[see Warnings and Precautions (5.4)]*.

Monitor hepatic function prior to and during treatment with efavirenz, lamivudine and tenofovir disoproxil fumarate tablets *[see Warnings and Precautions (5.9)]*.

2.2 Recommended Dosage for Adult and Pediatric Patients Weighing at Least 40 kg

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are a three-drug fixed-dose combination product containing 600 mg of efavirenz (EFV), 300 mg of lamivudine (3TC), and 300 mg of tenofovir disoproxil fumarate (TDF). The recommended dosage of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets in HIV-1-infected adults and pediatric patients who weigh at least 40 kg, and can swallow a solid tablet, is one tablet taken orally once daily. 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 (5.6) and Adverse Reactions (6.1)]*.

2.3 Not Recommended in Renal Impairment

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

2.4 Not Recommended in Moderate to Severe Hepatic Impairment

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are not recommended in patients with moderate or severe hepatic impairment (Child-Pugh B or C) *[see Warnings and Precautions (5.9) and Use in Specific Populations (8.7)]*.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 600 mg of efavirenz, 300 mg of lamivudine, and 300 mg of tenofovir disoproxil fumarate (equivalent to 245 mg of tenofovir disoproxil).

The tablets are white colored, capsule shaped, biconvex, film coated tablets, debossed with 'L65' on one side and plain on the other side.

4 CONTRAINDICATIONS

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are contraindicated:

- in patients with a previous hypersensitivity reaction (e.g., Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the components contained in the formulation *[see Warnings and Precautions (5.8)]*.
- when coadministered with elbasvir and grazoprevir *[see Warnings and Precautions (5.3) and Drug Interactions (7.5)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Severe Acute Exacerbation of Hepatitis B in Patients Coinfected with HIV-1 and HBV

Posttreatment Exacerbations of Hepatitis: All patients with HIV-1 should be tested for the presence of chronic hepatitis B virus (HBV) before initiating antiretroviral therapy *[see Dosage and Administration (2.1)]*. Discontinuation of anti-HBV therapy, including 3TC and TDF, may be associated with severe acute exacerbations of hepatitis B. Patients infected with HBV who discontinue efavirenz, lamivudine and tenofovir disoproxil fumarate should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted.

Important Differences Among Lamivudine-Containing Products: Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets contain a higher dose of the same active ingredient, 3TC, than EPIVIR-HBV® tablets. EPIVIR-HBV was developed for patients with chronic hepatitis B. The formulation and dosage of 3TC in EPIVIR-HBV are not appropriate for patients co-infected with HIV-1 and HBV. Safety and efficacy of 3TC have not been established for treatment of chronic hepatitis B in patients co-infected with HIV-1 and HBV.

If treatment with EPIVIR-HBV, TDF, or a tenofovir alafenamide (TAF)-containing product is prescribed for chronic hepatitis B for a patient with unrecognized or untreated HIV-1 infection, rapid emergence of HIV-1 resistance is likely to result because of the subtherapeutic dose and the inappropriateness of monotherapy HIV-1 treatment.

5.2 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 analogs and other antiretrovirals. Female sex and obesity may be risk factors for the development of lactic acidosis and severe hepatomegaly with steatosis in patients treated with antiretroviral nucleoside analogues. Treatment should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity, which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations.

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

The concomitant use of efavirenz, lamivudine and tenofovir disoproxil fumarate 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 and possible development of resistance.
- Possible clinically significant adverse reactions from greater exposures of concomitant drugs.

See Table 3 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 theraphy with efavirenz, lamivudine and tenofovir disoproxil fumarate; review concomitant medications during therapy with efavirenz, lamivudine and tenofovir disoproxil fumarate; and monitor for the adverse reactions associated with the concomitant drugs.

5.4 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, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients.

Avoid efavirenz, lamivudine and tenofovir disoproxil fumarate with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple non-steroidal anti-inflammatory drugs [NSAIDs]) *[see Drug Interactions (7.3)]*. Cases of acute renal failure after initiation of high-dose or multiple NSAIDs have been reported in HIV-infected patients with risk factors for renal dysfunction who appeared stable on 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 patients at risk of renal dysfunction.

5.5 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 1,008 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 EFV-treated and control-treated patients. One percent of EFV-treated patients discontinued or interrupted treatment because of one or more of these selected psychiatric symptoms.

There have also been occasional postmarketing reports of death by suicide, delusions, psychosis- like behavior, 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.

5.6 Nervous System Symptoms

Fifty-three percent (531/1,008) 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 1,008 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 (5.5)]*. Dosing at bedtime may improve the tolerability of these nervous system symptoms *[see Dosage and Administration (2.2)]*.

Late-onset neurotoxicity, including ataxia and encephalopathy (impaired consciousness, confusion, psychomotor slowing, psychosis, delirium), may occur months to years after beginning efavirenz therapy. Some events of late-onset neurotoxicity have occurred in patients with CYP2B6 genetic polymorphisms which are associated with increased efavirenz levels despite daily dosages of 600 mg of efavirenz. Patients presenting with signs and symptoms of serious neurologic adverse experiences should be evaluated promptly to assess the possibility that these events may be related to efavirenz use, and whether discontinuation of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets is warranted.

5.7 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)]*.

5.8 Skin and Systemic Hypersensitivity Reaction

In controlled clinical trials, 26% (266/1,008) of patients treated with 600 mg EFV experienced new-onset skin rash compared with 17% (111/635) of patients treated in control groups. Rash associated with blistering, moist desquamation, or ulceration occurred in 0.9% (9/1,008) 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% (17/1,008).

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)]*.

5.9 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 (2.1)]*. Consider discontinuing efavirenz, lamivudine and tenofovir disoproxil fumarate 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 if elevation of serum transaminases is accompanied by clinical signs or symptoms of hepatitis or hepatic decompensation.

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 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, generally in the presence of known medical history of seizures *[see Nonclinical Toxicology (13.2)]*. Caution should be taken in any patient with a history of seizures. Patients who are receiving concomitant anticonvulsant medications primarily metabolized by the liver, such as phenytoin and phenobarbital, may require periodic monitoring of plasma levels *[see Drug Interactions (7.5)]*.

5.12 Lipid Elevations

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

5.13 Bone Loss and Mineralization Effects

Bone Mineral Density (BMD): In clinical trials in HIV-1-infected adults, TDF was associated with slightly greater decreases in BMD and increases in biochemical markers of bone metabolism, suggesting increased bone turnover relative to comparators *[see Adverse Reactions (6.1)]*. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in subjects receiving TDF.

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. 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 one loss. If bone abnormalities are suspected then appropriate consultation should be obtained.

Mineralization Defects: Cases of osteomalacia associated with proximal renal tubulopathy, manifested as bone pain or pain in extremities and which may contribute to fractures, have been reported in association with TDF use *[see Adverse Reactions (6.2)]*. Arthralgia 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 TDF-containing products *[see Warnings and Precautions (5.4)]*.

5.14 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy, including EFV, 3TC, and TDF. 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, Guillain-Barre syndrome, and autoimmune hepatitis) 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 Fat Redistribution

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

5.16 QTc Prolongation

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

6 ADVERSE REACTIONS

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

- Exacerbations of Hepatitis B *[see Boxed Warning, Warnings and Precautions (5.1)]*.
- Lactic Acidosis/Severe Hepatomegaly with Steatosis *[see Warnings and Precautions (5.2)]*.
- New Onset or Worsening Renal Impairment *[see Warnings and Precautions (5.4)]*.
- Psychiatric Symptoms *[see Warnings and Precautions (5.5)]*.
- Nervous System Symptoms *[see Warnings and Precautions (5.6)]*.
- Skin and Systemic Hypersensitivity Reaction *[see Warnings and Precautions (5.8)]*.
- Hepatotoxicity *[see Warnings and Precautions (5.9)]*.
- Pancreatitis *[see Warnings and Precautions (5.10)]*.
- Bone Loss and Mineralization Effects *[see Warnings and Precautions (5.13)]*.
- Immune Reconstitution Syndrome *[see Warnings and Precautions (5.14)]*.
- Fat Redistribution *[see Warnings and Precautions (5.15)]*.

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, the adverse reaction rates observed in 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

Clinical Trials in Treatment-Naïve HIV-1 Infected Adult Subjects

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 (Grade 2 to 4) occurring in greater than or equal to 5% of subjects treated in any treatment group.

Table 1. Selected Adverse Reactions[a] (Grades 2 to 4) Reported in ≥ 5% in Any Treatment Group in Trial 903 (0 to 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, vesiculobullous 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.

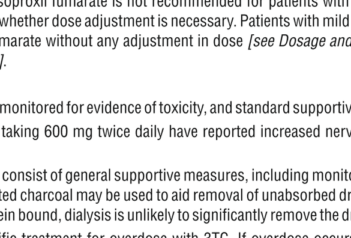
Laboratory Abnormalities: Table 2 provides a list of laboratory abnormalities (Grades 3 to 4) observed in Trial 903. With the exception of fasting cholesterol and fasting triglyceride elevations that were more common in the d4T group (40% and 9%) compared with the TDF group (19% and 1%) respectively, laboratory abnormalities observed in this trial occurred with similar frequency in the TDF and d4T treatment arms.

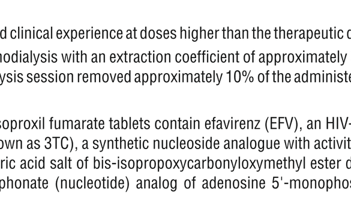
Table 2. Grade 3 to 4 Laboratory Abnormalities Reported in ≥ 1% of Patients Randomized to Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate in Study 903 (0 to 144 Weeks)

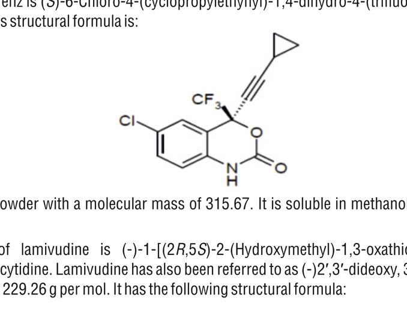
	TDF + 3TC + EFV	d4T + 3TC + EFV
	N = 299	N = 301
Any ≥ Grade 3 Laboratory Abnormality	36%	42%
Fasting Cholesterol (> 240 mg/dL)	19%	40%
Creatine Kinase (M: > 990 U/L; F: > 845 U/L)	12%	12%
Serum Amylase (> 175 U/L)	9%	8%
AST (M: > 180 U/L; F: > 170 U/L)	5%	7%
ALT (M: > 215 U/L; F: > 170 U/L)	4%	5%
Hematuria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

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)]*.

[illegible]







[illegible]

Patient Information

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

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 infection.** If you have Human Immunodeficiency Virus type 1 (HIV-1) and Hepatitis B Virus (HBV) infection, 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. Your healthcare provider will test you for HBV infection before you start treatment with efavirenz, lamivudine and tenofovir disoproxil fumarate tablets.
  - It is not known if efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are safe and effective in people who have both HIV-1 and HBV infection.
  - 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 are all gone.
  - **Do not stop efavirenz, lamivudine and tenofovir disoproxil fumarate tablets without first talking to 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.

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

What are efavirenz, lamivudine and tenofovir disoproxil fumarate tablets?

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are a prescription medicine that is used without other antiretroviral medicines to treat Human Immunodeficiency Virus-1 (HIV-1) in adults and children weighing at least 88 pounds (40 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

[illegible]

SS ARTS Graphic Designers	**Product Name:** ELT 600 mg/300 mg/300 mg	**Component:** Leaflet
	Market: USA	**No. of Colours:** 01
Version No: 07	**Manufacturing Location:** --------	**List. of Colours:** Black
Date: 29.05.2020	**SAP Code:** 2xxxxx	

Change History:
New Artwork (18.11.2019)
Correction Done (20.11.2019)
Correction Done (22.11.2019)
Correction Done (25.11.2019)
Correction Done (26.05.2020)
Correction Done (27.05.2020)
Correction Done (29.05.2020)

37 mm 37 mm

2000595

500 x 800 mm
PC : 181

12.2 Pharmacodynamics

Cardiac Electrophysiology: The effect of EFV on the QTc interval was evaluated in an open-label, positive and placebo-controlled, fixed single sequence 3-period, 3-treatment crossover QT study in 58 healthy subjects enriched for CYP2B6 polymorphisms. The mean C_{max} of EFV in subjects with CYP2B6 *6/*6 genotype following the administration of 600 mg daily dose for 14 days was 2.25-fold the mean C_{max} observed in subjects with CYP2B6 *1/*1 genotype. A positive relationship between EFV concentration and QTc prolongation was observed. Based on the concentration-QTc relationship, the mean QTc prolongation and its upper bound 90% confidence interval are 8.7 ms and 11.3 ms in subjects with CYP2B6*6/*6 genotype following the administration of 600 mg daily dose for 14 days *[see Warnings and Precautions (5.16)]*.

12.3 Pharmacokinetics

The effect of food on efavirenz, lamivudine and tenofovir disoproxil fumarate has not been evaluated.

Efavirenz: In HIV-1-infected subjects, time-to-peak plasma concentrations were approximately 3 to 5 hours and steady-state plasma concentrations were reached in 6 to 10 days. EFV is highly bound (approximately 99.5 to 99.75%) to human plasma proteins, predominantly albumin. Following administration of ^{14}C-labeled EFV, 14 to 34% of the dose was recovered in the urine (mostly as metabolites) and 16 to 61% was recovered in feces (mostly as parent drug). *In vitro* studies suggest CYP3A and CYP2B6 are the major isozymes responsible for EFV metabolism. EFV has been shown to induce CYP enzymes, resulting in induction of its own metabolism. EFV has a terminal half-life of 52 to 76 hours after single doses and 40 to 55 hours after multiple doses.

Lamivudine: After oral administration of 2 mg/kg of 3TC twice a day to 9 adults with HIV-1, the peak serum 3TC concentration (C_{max}) was 1.5 ± 0.5 mcg/mL (mean ± SD). The area under the plasma concentration versus time curve (AUC) and C_{max} increased in proportion to oral dose over the range from 0.25 to 10 mg/kg and absolute bioavailability in 12 adult patients was 86% ± 16% (mean ± SD) for the 150-mg tablet and 87% ± 13% for the oral solution. Binding of 3TC to human plasma proteins is low (< 36%). Within 12 hours after a single oral dose of 3TC in 6 HIV-1-infected adults, 5.2% ± 1.4% (mean ± SD) of the dose was excreted as the trans-sulfoxide metabolite in the urine. The majority of 3TC is eliminated unchanged in urine by active organic cationic secretion and the observed mean elimination half-life ($t_{1/2}$) ranged from 5 to 7 hours in most single-dose studies with serum sampling for 24 hours after dosing.

Tenofovir Disoproxil Fumarate: Following oral administration of a single 300 mg dose of TDF to HIV-1-infected subjects in the fasted state, maximum serum concentrations (C_{max}) were achieved in 1.0 ± 0.4 hrs (mean ± SD) and C_{max} and AUC values were 296 ± 90 ng/mL and 2,287 ± 685 ng•hr/mL, respectively. The oral bioavailability of tenofovir from TDF in fasted subjects is approximately 25%. Less than 0.7% of tenofovir binds to human plasma proteins in vitro and the binding is independent of concentration over the range of 0.01 to 25 mcg/mL. Approximately 70 to 80% of the intravenous dose of tenofovir is recovered as unchanged drug in the urine. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion with a renal clearance in adults with normal renal function of 243 ± 33 mL/min (mean ± SD). Following a single oral dose, the terminal elimination half-life of tenofovir is approximately 17 hours.

Special Populations:

Race:

Efavirenz and Lamivudine: There are no significant or clinically relevant racial differences in EFV and 3TC pharmacokinetics.

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

Gender: There are no significant or clinically relevant gender differences in the pharmacokinetics of EFV, 3TC, and TDF.

Geriatric Patients: The pharmacokinetics of 3TC and TDF have not been studied in patients over 65 years of age.

Patients with Renal Impairment: [See Use in Specific Populations (8.6).]

Efavirenz: The pharmacokinetics of EFV have not been studied in patients with renal impairment.

Lamivudine: The pharmacokinetics of 3TC are altered in subjects with renal impairment (Table 4).

Table 4. Pharmacokinetic Parameters (Mean ± SD) after a Single 300-mg Oral Dose of 3TC in Subjects with Varying Degrees of Renal Function

Parameter	Creatinine Clearance Criterion (Number of Subjects)		
	> 60 mL/min (n = 6)	10 to 30 mL/min (n = 4)	< 10 mL/min (n = 6)
Creatinine clearance (mL/min)	111 ± 14	28 ± 8	6 ± 2
C_{max} (mcg/mL)	2.6 ± 0.5	3.6 ± 0.8	5.8 ± 1.2
AUC_∞ (mcg•h/mL)	11.0 ± 1.7	48.0 ± 19	157 ± 74
Cl/F (mL/min)	464 ± 76	114 ± 34	36 ± 11

Tenofovir Disoproxil Fumarate: The pharmacokinetics of TDF are altered in subjects with renal impairment *[see Warnings and Precautions (5.4)]*. In subjects with creatinine clearance below 50 mL/min or with end-stage renal disease (ESRD) requiring dialysis, C_{max}, and $AUC_{0-\infty}$ of tenofovir were increased.

Table 5. Pharmacokinetic Parameters (Mean ± SD) of Tenofovir After a Single 300-mg Oral Dose of TDF in Subjects with Varying Degrees of Renal Function

Baseline Creatinine Clearance (mL/min)	> 80 (N = 3)	50 to 80 (N = 10)	30 to 49 (N = 8)	12 to 29 (N = 11)
C_{max} (mcg/mL)	0.34 ± 0.03	0.33 ± 0.06	0.37 ± 0.16	0.60 ± 0.19
$AUC_{0-\infty}$ (mcg•hr/mL)	2.18 ± 0.26	3.06 ± 0.93	6.01 ± 2.50	15.98 ± 7.22
CL/F (mL/min)	1043.7 ± 115.4	807.7 ± 279.2	444.4 ± 209.8	177.0 ± 97.1
CL_{renal} (mL/min)	243.5 ± 33.3	168.6 ± 27.5	100.6 ± 27.5	43.0 ± 31.2

Patients with Hepatic Impairment:

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

Lamivudine: The pharmacokinetic properties of 3TC have been determined in adults with impaired hepatic function. Pharmacokinetic parameters were not altered by diminishing hepatic function. Safety and efficacy of 3TC have not been established in the presence of decompensated liver disease.

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

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

Efavirenz: EFV has been shown *in vivo* to cause hepatic enzyme induction, thus increasing the biotransformation of some drugs metabolized by CYP3A and CYP2B6. *In vitro* studies have shown that EFV inhibited CYP isozymes 2C9, 2C19, and 3A4 with K_i values (8.5 to 17 mcM) in the range of observed EFV plasma concentrations. In *in vitro* studies, EFV did not inhibit CYP2E1 and inhibited CYP2D6 and CYP1A2 (K_i values 82 to 160 mcM) only at concentrations well above those achieved clinically. Coadministration of EFV with drugs primarily metabolized by 2C9, 2C19, and 3A isozymes may result in altered plasma concentrations of the coadministered drug. Drugs which induce CYP3A activity would be expected to increase the clearance of EFV resulting in lowered plasma concentrations.

Drug interaction studies were performed with EFV and other drugs likely to be coadministered or drugs commonly used as probes for pharmacokinetic interaction. The effects of coadministration of EFV on the C_{max}, AUC, and C_{min} are summarized in Table 6 (effect of EFV on other drugs) and Table 7 (effect of other drugs on EFV). For information regarding clinical recommendations see *Drug Interactions (7.5)*.

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

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Coadministered Drug (mean % change)		
				C_{max} (90% CI)	AUC (90% CI)	C_{min} (90% CI)
Boceprevir	800 mg tid x 6 days	600 mg qd x 16 days	NA	↓ 8% (↓ 22 to ↑ 8%)	↓ 19% (11 to 25%)	↓ 44% (26 to 58%)
Simeprevir	150 mg qd x 14 days	600 mg qd x 14 days	23	↓ 51% (↓ 46 to ↓ 56%)	↓ 71% (↓ 67 to ↓ 74%)	↓ 91% (↓ 88 to ↓ 92%)
Ledipasvir/ Sofosbuvir[d]	90/400 mg qd x 14 days	600 mg qd x 14 days	15			
Ledipasvir				↓ 34 (↓ 25 to ↓ 41)	↓ 34 (↓ 25 to ↓ 41)	↓ 34 (↓ 24 to ↓ 43)
Sofosbuvir				↔	↔	NA
GS-331007[e]				↔	↔	↔
Sofosbuvir[f]	400 mg qd single dose	600 mg qd x 14 days	16	↓ 19 (↓ 40 to ↑10)	↔	NA
GS-331007[e]				↓ 23 (↓ 16 to ↓ 30)	↓ 16 (↓ 24 to ↓ 8)	NA
Sofosbuvir/ Velpatasvir[g]	400/100 mg qd x 14 days	600 mg qd x 14 days	14			
Sofosbuvir				↑ 38 (↑14 to ↑67)	↔	NA
GS-331007[e]				↓ 14 (↓ 20 to ↓ 7)	↔	↔
Velpatasvir				↓ 47 (↓ 57 to ↓ 36)	↓ 53 (↓ 61 to ↓ 43)	↓ 57 (↓ 64 to ↓ 48)
Azithromycin	600 mg single dose	400 mg qd x 7 days	14	↑ 22% (4 to 42%)	↔	NA
Clarithromycin	500 mg q12h x 7 days	400 mg qd x 7 days	11	↑ 26% (15 to 35%)	↓ 39% (30 to 46%)	↓ 53% (42 to 63%)
14-OH metabolite				↑ 49% (32 to 69%)	↑ 34% (18 to 53%)	↑ 26% (9 to 45%)
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 to 51%)	↓ 39% (21 to 53%)	↓ 44% (27 to 58%)
Hydroxy-itraconazole				↓ 35% (12 to 52%)	↓ 37% (14 to 55%)	↓ 43% (18 to 60%)
Posaconazole	400 mg (oral suspension) bid x 10 and 20 days	400 mg qd x 10 and 20 days	11	↓ 45% (34 to 53%)	↓ 50% (40 to 57%)	NA
Rifabutin	300 mg qd x 14 days	600 mg qd x 14 days	9	↓ 32% (15 to 46%)	↓ 38% (28 to 47%)	↓ 45% (31 to 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 to 7	300 mg qd x 7 days	NA	↓ 36%[b] (21 to 49%)	↓ 55%[b] (45 to 62%)	NA
	400 mg po q12h days 2 to 7	300 mg qd x 7 days	NA	↑ 23%[b] (↓ 1 to ↑ 53%)	↓ 7%[b] (↓ 23 to ↑ 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
dihydroartemisinin				↓ 38%	↓ 46%	NA
lumefantrine				↔	↓ 21%	NA
Atorvastatin	10 mg qd x 4 days	600 mg qd x 15 days	14	↓ 14% (1 to 26%)	↓ 43% (34 to 50%)	↓ 69% (49 to 81%)
Total active (including metabolites)				↓ 15% (2 to 26%)	↓ 32% (21 to 41%)	↓ 48% (23 to 64%)
Pravastatin	40 mg qd x 4 days	600 mg qd x 15 days	13	↓ 32% (↓ 59 to ↑ 12%)	↓ 44% (26 to 57%)	↓ 19% (0 to 35%)
Simvastatin	40 mg qd x 4 days	600 mg qd x 15 days	14	↓ 72% (63 to 79%)	↓ 68% (62 to 73%)	↓ 45% (20 to 62%)
Total active (including metabolites)				↓ 68% (55 to 78%)	↓ 60% (52 to 68%)	NA[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 to 24%)	↓ 27% (20 to 33%)	↓ 35% (24 to 44%)
Epoxide metabolite				↔	↔	↓ 13% (↓ 30 to ↑ 7%)
Cetirizine	10 mg single dose	600 mg qd x 10 days	11	↓ 24% (18 to 30%)	↔	NA
Diltiazem	240 mg x 21 days	600 mg qd x 14 days	13	↓ 60% (50 to 68%)	↓ 69% (55 to 79%)	↓ 63% (44 to 75%)
Desacetyl diltiazem				↓ 64% (57 to 69%)	↓ 75% (59 to 84%)	↓ 62% (44 to 75%)
N-monodes-methyl diltiazem				↓ 28% (7 to 44%)	↓ 37% (17 to 52%)	↓ 37% (17 to 52%)
Ethinyl estradiol/ Norgestimate	0.035 mg/0.25 mg x 14 days	600 mg qd x 14 days				
Ethinyl estradiol			21	↔	↔	↔
Norelgestromine			21	↓ 46% (39 to 52%)	↓ 64% (62 to 67%)	↓ 82% (79 to 85%)
Levonorgestrel			6	↓ 80% (77 to 83%)	↓ 83% (79 to 87%)	↓ 86% (80 to 90%)
Lorazepam	2 mg single dose	600 mg qd x 10 days	12	↑ 16% (2 to 32%)	↔	NA
Methadone	Stable maintenance 35 to 100 mg daily	600 mg qd x 14 to 21 days	11	↓ 45% (25 to 59%)	↓ 52% (33 to 66%)	NA
Bupropion	150 mg single dose (sustained-release)	600 mg qd x 14 days	13	↓ 34% (21 to 47%)	↓ 55% (48 to 62%)	NA
Hydroxy-bupropion				↑ 50% (20 to 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 to 40%)	↓ 39% (27 to 50%)	↓ 46% (31 to 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 7. Effect of Coadministered Drug on Efavirenz Plasma C_{max}, AUC, and C_{min}

Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	Efavirenz (mean % change)		
				C_{max} (90% CI)	AUC (90% CI)	C_{min} (90% CI)
Boceprevir	800 mg tid x 6 days	600 mg qd x 16 days	NA	↑ 11% (2 to 20%)	↑ 20% (15 to 26%)	NA
Simeprevir	150 mg qd x 14 days	600 mg qd x 14 days	23	↔	↓ 10% (5 to 15%)	↓ 13% (7 to 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 to 19%)	↔	↔
Fluconazole	200 mg x 7 days	400 mg qd x 7 days	10	↔	↑ 16% (6 to 26%)	↑ 22% (5 to 41%)
Itraconazole	200 mg q12h x 14 days	600 mg qd x 28 days	16	↔	↔	↔
Rifabutin	300 mg qd x 14 days	600 mg qd x 14 days	11	↔	↔	↓ 12% (↓ 24 to ↑1%)
Rifampin	600 mg x 7 days	600 mg qd x 7 days	12	↓ 20% (11 to 28%)	↓ 26% (15 to 36%)	↓ 32% (15 to 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 to 7	300 mg qd x 7 days	NA	↓ 14%[b] (7 to 21%)	↔[b]	NA
	400 mg po q12h days 2 to 7	300 mg qd x 7 days	NA	↔[b]	↑ 17%[b] (6 to 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 to ↑ 8%)	↔	↓ 12% (↓ 25 to ↑ 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 to 26%)	↓ 36% (32 to 40%)	↓ 47% (41 to 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 to 26%)	↑ 11% (5 to 18%)	↑ 13% (1 to 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 to 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.

Lamivudine: 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.

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.

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 $AUC_{(\infty)}$, and 28%, 52%, and 55% in the C_{max} of lamivudine, 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 3TC 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 3TC AUC_∞, a decrease of 29% ± 13% in 3TC 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 treating PCP.

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

Table 8 summarizes pharmacokinetic effects of coadministered drug on tenofovir pharmacokinetics. No clinically significant drug interactions have been observed between tenofovir and ribavirin.

Table 8. 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[c,f]	90/400 once daily x 10 days	24	↑ 47 (↑ 37 to ↑ 58)	↑ 35 (↑ 29 to ↑ 42)	↑ 47 (↑ 38 to ↑ 57)
Ledipasvir/ Sofosbuvir[c,g]		23	↑ 64 (↑ 54 to ↑ 74)	↑ 50 (↑ 42 to ↑ 59)	↑ 59 (↑ 49 to ↑ 70)
Ledipasvir/ Sofosbuvir[c]	90/400 once daily x 14 days	15	↑ 79 (↑ 56 to ↑104)	↑ 98 (↑ 77 to ↑123)	↑ 163 (↑ 132 to ↑ 197)
Sofosbuvir/ Velpatasvir[h]	400/100 once daily	24	↑ 44 (↑ 33 to ↑55)	↑ 40 (↑ 34 to ↑46)	↑ 84 (↑ 76 to ↑ 92)
Sofosbuvir/ Velpatasvir[i]	400/100 once daily	30	↑ 46 (↑ 39 to ↑54)	↑ 40 (↑ 34 to ↑45)	↑ 70 (↑ 61 to ↑ 79)
Sofosbuvir/ Velpatasvir/ Voxilaprevir[j]	400/100/100 + Voxilaprevir[k] 100 once daily	29	↑ 48 (↑ 36 to ↑61)	↑ 39 (↑32 to ↑46)	↑47 (↑ 38 to ↑ 56)
Sofosbuvir[d]	400 single dose	16	↑ 25 (↑ 8 to ↑ 45)	↔	↔
Tacrolimus	0.05 mg/kg twice daily x 7 days	21	↑ 13 (↑ 1 to ↑ 27)	↔	↔

[a] Subjects received tenofovir disoproxil fumarate 300 mg once daily.
[b] Increase = ↑; Decrease = ↓; No Effect = ↔; NC = Not Calculated
[c] Study conducted with efavirenz/emtricitabine/tenofovir disoproxil fumarate coadministered with ledipasvir/sofosbuvir.
[d] Study conducted with efavirenz/emtricitabine/tenofovir disoproxil fumarate coadministered with sofosbuvir.
[e] Data generated from simultaneous dosing with ledipasvir/sofosbuvir. Staggered administration (12 hours apart) provide similar results.
[f] Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine/tenofovir DF.
[g] Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/tenofovir DF.
[h] 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.
[i] Administered as raltegravir + FTC/TDF.
[j] Comparison based on exposures when administered as darunavir + ritonavir + FTC/TDF.
[k] Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

12.4 Microbiology

Mechanism of Action: *Efavirenz:* 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.

Lamivudine: 3TC is a synthetic nucleoside analogue with activity against HIV-1 and HBV. 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.

Tenofovir Disoproxil Fumarate: 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 (TDF-DP), an obligate chain terminator. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase (RT) and HBV RT by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Antiviral Activity: *Efavirenz:* 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.

Lamivudine: The antiviral activity of 3TC against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes (PBMCs) using standard susceptibility assays. EC_{50} values were in the range of 3 to 15,000 nM. (1 mcM = 0.23 mcg/mL). The median EC_{50} values of 3TC 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 to G and group O viruses (n = 3 except n = 2 for clade B), respectively. The EC_{50} values against HIV-2 isolates (n = 4) ranged from 3 to 120 nM in PBMCs. 3TC was not antagonistic to all tested anti-HIV agents. Ribavirin (50 mcM) used in the treatment of chronic HCV infection decreased the anti-HIV-1 activity of 3TC by 3.5-fold in MT-4 cells.

Tenofovir Disoproxil Fumarate: The antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The EC_{50} (50% effective concentration) values for tenofovir were in the range of 0.04 mcM to 8.5 mcM. Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC_{50} values ranged from 0.5 mcM to 2.2 mcM) and strain-specific activity against HIV-2 (EC_{50} values ranged from 1.6 mcM to 5.5 mcM). Please see the full prescribing information for VIREAD® for information regarding the inhibitory activity of TDF against HBV.

Resistance: *Efavirenz:* In cell culture, HIV-1 isolates with reduced susceptibility to EFV (> 380-fold increase in EC_{90} value) emerged rapidly in the presence of drug. Genotypic characterization of these viruses identified single amino acid substitutions L100I or V179D, double substitutions L100I/V108I, and triple substitutions L100I/V179D/Y181C in reverse transcriptase.

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.

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

Tenofovir Disoproxil Fumarate: HIV-1 isolates with reduced susceptibility to tenofovir have been selected in cell culture. These viruses expressed a K65R substitution in RT and showed a 2- to 4-fold reduction in susceptibility to tenofovir. In addition, a K70E substitution in HIV-1 RT has been selected by tenofovir and results in low-level reduced susceptibility to tenofovir. K65R substitutions developed in some subjects failing a tenofovir disoproxil fumarate regimen.

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

Lamivudine: Cross-resistance among 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.

Tenofovir Disoproxil Fumarate: Cross-resistance among certain HIV-1 NRTIs has been observed. The K65R and K70E substitutions selected by tenofovir are also selected in some HIV-1-infected subjects treated with abacavir or didanosine. HIV-1 isolates with the K65R substitution also showed reduced susceptibility to FTC 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 VIREAD. Limited data are available for patients whose virus expressed a Y115F substitution (N = 3), Q151M substitution (N = 2), or T69 insertion (N = 4), all of whom had a reduced response.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Efavirenz: Long-term carcinogenicity studies in mice and rats were carried out with efavirenz. Mice were dosed with 0, 25, 75, 150, or 300 mg/kg/day for 2 years. Incidences of hepatocellular adenomas and carcinomas and pulmonary alveolar/bronchiolar adenomas were increased above background in females. No increases in tumor incidence above background were seen in males. There was no NOAEL in female established for this study because tumor findings occurred at all doses. AUC at the NOAEL (150 mg/kg) in the males was approximately 0.9 times that in humans at the recommended clinical dose. In the rat study, no increases in tumor incidence were observed at doses up to 100 mg/kg/day, for which AUCs were 0.1 (males) or 0.2 (females) times those in humans at the recommended clinical dose.

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.

Lamivudine: 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 not mutagenic in a microbial mutagenicity assay, in an *in vitro* cell transformation assay, in a rat micronucleus test, in a rat bone marrow cytogenetic assay, and in assay for unscheduled DNA synthesis in rat liver. 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. In a study of reproductive performance, 3TC administered to rats at doses up to 4,000 mg per kg per day, producing plasma levels 47 to 70 times those in humans, revealed no evidence of impaired fertility and no effect on the survival, growth, and development to weaning of the offspring.

Tenofovir Disoproxil Fumarate: Long-term oral carcinogenicity studies of 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

Efavirenz: 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)]*.

Tenofovir Disoproxil Fumarate: 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 600 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 Trial 903.

Trial 903: Data through 144 weeks are reported for Trial 903, a double-blind, active-controlled multicenter trial comparing EFV 600 mg + 3TC 300 mg + TDF 300 mg vs. EFV 600 mg + 3TC 300 mg + stavudine (d4T) 40 mg in 600 antiretroviral-naïve subjects. Subjects had a mean age of 36 years (range 18 to 64); 74% were male, 64% were Caucasian, and 20% were Black. The mean baseline CD4+ cell count was 279 cells/mm^3 (range 3 to 956) and median baseline plasma HIV-1 RNA was 77,600 copies/mL (range 417 to 5,130,000). Subjects were stratified by baseline HIV-1 RNA and CD4+ cell count. Forty-three percent of subjects had baseline viral loads > 100,000 copies/mL and 39% had CD4+ cell counts < 200 cells/mm^3. Table 9 provides treatment outcomes through 48 and 144 weeks.

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

Outcomes	At Week 48		At Week 144	
	EFV + 3TC + TDF (N = 299)	EFV + 3TC + d4T (N = 301)	EFV + 3TC + TDF (N = 299)	EFV + 3TC + d4T (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 < 400 copies/mL at Week 144 was similar between the two treatment groups for the population stratified at baseline on the basis of HIV-1 RNA concentration (> or ≤ 100,000 copies/mL) and CD4+ cell count (< or ≥ 200 cells/mm^3). Through 144 weeks of therapy, 62% and 58% of subjects in the TDF and 4dT arms, respectively, achieved and maintained confirmed HIV-1 RNA < 50 copies/mL. The mean increase from baseline in CD4+ cell count was 263 cells/mm^3 for the TDF arm and 283 cells/mm^3 for the 4dT arm.

Through 144 weeks, 11 subjects in the TDF group and 9 subjects in the 4dT group experienced a new CDC Class C event.

16 HOW SUPPLIED/STORAGE AND HANDLING

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets 600 mg/300 mg/300 mg are white colored, capsule shaped, biconvex, film coated tablets, debossed with 'L65' on one side and plain on the other side. They are available as follows:

Bottles of 30 NDC 42385-928-30
Bottles of 90 NDC 42385-928-90

Store at 20° to 25°C (68° to 77°F), excursions permitted between 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature.]
Keep the bottle tightly closed.
Dispense in original container.
Do not use if seal over bottle opening is broken or missing.

17 PATIENT COUNSELING INFORMATION

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

Drug Interactions: Efavirenz, lamivudine and tenofovir disoproxil fumarate 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)]*.

Post Treatment Acute Exacerbation of Hepatitis B in Patients with HBV Co-Infection: Inform patients that severe acute exacerbations of hepatitis have been reported in patients who are infected with HBV or coinfected with HBV and HIV-1 and have discontinued 3TC and TDF, components of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. Test patients with HIV-1 for hepatitis B virus (HBV) before initiating antiretroviral therapy. In patients with chronic hepatitis B, it is important to obtain HIV antibody testing prior to initiating 3TC and TDF, components of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets *[see Warnings and Precautions (5.1)]*.

Lactic Acidosis and Severe Hepatomegaly: Inform patients that lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Treatment with efavirenz, lamivudine and tenofovir disoproxil fumarate should be suspended in any patient who develops clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity (including nausea, vomiting, unusual or unexpected stomach discomfort, and weakness) *[see Warnings and Precautions (5.2)]*.

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 impaired renal function (i.e., creatinine clearance less than 50 mL/min) or patients with end-stage renal disease (ESRD) requiring hemodialysis to avoid efavirenz, lamivudine and tenofovir disoproxil fumarate with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple NSAIDs) for patients *[see Dosage and Administration (2.3), Warnings and Precautions (5.4)]*.

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 (5.5)]*. 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 (5.6)]*. 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 used concomitantly with alcohol or psychoactive drugs. Instruct patients that if they experience NSS they should avoid potentially hazardous tasks such as driving or operating machinery.

Inform patients that there is a risk of developing late-onset neurotoxicity, including ataxia and encephalopathy, which may occur months to years after beginning efavirenz therapy *[see Warnings and Precautions (5.6)]*.

Embryo-Fetal Toxicity: Advise female patients that 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 to use effective contraception as well as a barrier method during treatment with efavirenz, lamivudine and tenofovir disoproxil fumarate and for 12 weeks after discontinuation of use. Advise patients to contact their healthcare provider if they plan to become pregnant, become pregnant, or if pregnancy is suspected during treatment with efavirenz, lamivudine and tenofovir disoproxil fumarate *[see Warnings and Precautions (5.7), Use in Specific Populations (8.1, 8.3)]*.

Rash: Inform patients that rash is a common side effect of EFV *[see Warnings and Precautions (5.8)]*. 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 (5.9)]*.

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

Convulsions: Advise patients that convulsions have been observed in patients receiving EFV, a component of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, generally in patients with known medical history of seizures *[see Warnings and Precautions (5.11)]*.

Lipid Elevations: Advise patients 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 *[see Warnings and Precautions (5.12)]*.

Bone Loss and Mineralization Effects: Inform patients that decreases in bone mineral density have been observed with the use of 3TC and TDF, components of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, in patients with HIV *[see Warnings and Precautions (5.13)]*.

Immune Reconstitution Syndrome: Advise patients to inform their healthcare provider immediately of any symptoms of infection, as in some patients with advanced HIV infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started *[see Warnings and Precautions (5.14)]*.

Fat Redistribution: Inform patients that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy, including efavirenz, lamivudine and tenofovir disoproxil fumarate, and that the cause and long-term health effects of these conditions are not known at this time *[see Warnings and Precautions (5.15)]*.

Administration Instructions: Inform patients that it is important to take efavirenz, lamivudine and tenofovir disoproxil fumarate tablets once daily on a regular dosing schedule on an empty stomach, preferably at bedtime, and to avoid missing doses as it can result in development of resistance. Advise patients if a dose is missed, take it as soon as possible unless it is almost time for the next dose. Also advise patients that dosing at bedtime may improve the tolerability of nervous system symptoms *[see Dosage and Administration (2.2)]*.

Pregnancy Registry: Advise patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes in women exposed to efavirenz, lamivudine and tenofovir disoproxil fumarate *[see Use in Specific Populations (8.1)]*.

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

Brands listed are the trademarks of their respective owners and are not trademarks of Laurus Labs Limited or Laurus Generics Inc.

Manufactured for:
Laurus Generics Inc.
400 Connell Drive
Suite 5200
Berkeley Heights, NJ 07922

Manufactured by:
Laurus Labs Limited
Visakhapatnam-531011
India

Patient Information
Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate
(ef-a-vir-enz, la-MIV-ue-deen and ten-OF-oh-vir DYE-soe-PROX-il FUE-ma-rate)
Tablets

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 infection.** If you have Human Immunodeficiency Virus type 1 (HIV-1) and Hepatitis B Virus (HBV) infection, 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. Your healthcare provider will test you for HBV infection before you start treatment with efavirenz, lamivudine and tenofovir disoproxil fumarate tablets.
  - It is not known if efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are safe and effective in people who have both HIV-1 and HBV infection.
  - 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 are all gone.
  - **Do not stop efavirenz, lamivudine and tenofovir disoproxil fumarate tablets without first talking to 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.

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

What are efavirenz, lamivudine and tenofovir disoproxil fumarate tablets?

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are a prescription medicine that is used without other antiretroviral medicines to treat Human Immunodeficiency Virus-1 (HIV-1) in adults and children weighing at least 88 pounds (40 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 think you may be pregnant or become pregnant during treatment with efavirenz, lamivudine and tenofovir disoproxil fumarate tablets.
  - Females who are able to become pregnant should use effective birth control 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.
  - If you are able to become pregnant, your healthcare provider should do a pregnancy test before you start efavirenz, lamivudine and tenofovir disoproxil fumarate tablets.

  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. If it is almost time for your next dose of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, do not take the missed dose. Take the next dose at your regular time.
- 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?"**
- **Build-up of an acid in your blood (lactic acidosis).** Lactic acidosis can happen in some people who take efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. Lactic acidosis is a serious medical emergency that can lead to death. **Call 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
- **Severe liver problems** can happen in people who take efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. In some cases, these 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

You may be more likely to get lactic acidosis or serious liver problems if you are female or very overweight (obese).

- **New or worse kidney problems, including kidney failure.** Your healthcare provider may 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
- **Nervous system symptoms** are common in people who take efavirenz, lamivudine and tenofovir disoproxil fumarate tablets and 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. Some symptoms may occur months to years after beginning efavirenz, lamivudine and tenofovir disoproxil fumarate tablets therapy. These symptoms may become worse if you drink alcohol, take a medicine for mental health problems, or use certain street drugs during treatment with efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. Symptoms may include:
  - dizziness
  - trouble sleeping
  - unusual dreams
  - trouble concentrating
  - drowsiness
  - lack of coordination or balance

If you have dizziness, trouble concentrating or drowsiness, do not drive a car, use machinery, or do anything that needs you to be alert.
Some nervous system symptoms (e.g., confusion, slow thoughts and physical movement, and delusions [false beliefs] or hallucinations [seeing or hearing things that others do not see or hear]) may occur months to years after beginning efavirenz, lamivudine and tenofovir disoproxil fumarate tablets therapy. Promptly contact your health care provider should any of these symptoms occur.

- **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
- **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.
- **Changes in body fat** can happen in some people who take HIV-1 medicines. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the main part of your body (trunk). Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known.
- **Changes in 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.

The most common side effects of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are:

- trouble concentrating
- headache
- not feeling well
- nasal signs and symptoms
- rash
- trouble sleeping
- depression
- cough
- abnormal dreams
- nausea
- tiredness
- diarrhea
- dizziness
- pain
- weakness

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 at 20° to 25°C (68° to 77°F).
- Keep efavirenz, lamivudine and tenofovir disoproxil fumarate tablets in the original container.

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 ingredients: efavirenz USP, lamivudine USP, and tenofovir disoproxil fumarate

Inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, lactose anhydrous, magnesium stearate, microcrystalline cellulose, pregelatinized starch, polyethylene glycol, polyvinyl alcohol, sodium lauryl sulfate, talc and titanium dioxide.

Brands listed are the trademarks of their respective owners and are not trademarks of Laurus Labs Limited or Laurus Generics Inc.

For more information, call Laurus Generics Inc. at 1-833-3-LAURUS (1-833-352-8787).

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

Manufactured for:
Laurus Generics Inc.
400 Connell Drive
Suite 5200
Berkeley Heights, NJ 07922

Manufactured by:
Laurus Labs Limited
Visakhapatnam-531011
India

Revised: 11/2019

You may be more likely to get lactic acidosis or serious liver problems if you are female or very overweight (obese).

- **New or worse kidney problems, including kidney failure.** Your healthcare provider may 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
- **Nervous system symptoms** are common in people who take efavirenz, lamivudine and tenofovir disoproxil fumarate tablets and 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. Some symptoms may occur months to years after beginning efavirenz, lamivudine and tenofovir disoproxil fumarate tablets therapy. These symptoms may become worse if you drink alcohol, take a medicine for mental health problems, or use certain street drugs during treatment with efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. Symptoms may include:
  - dizziness
  - trouble sleeping
  - unusual dreams
  - trouble concentrating
  - drowsiness
  - lack of coordination or balance

If you have dizziness, trouble concentrating or drowsiness, do not drive a car, use machinery, or do anything that needs you to be alert.
Some nervous system symptoms (e.g., confusion, slow thoughts and physical movement, and delusions [false beliefs] or hallucinations [seeing or hearing things that others do not see or hear]) may occur months to years after beginning efavirenz, lamivudine and tenofovir disoproxil fumarate tablets therapy. Promptly contact your health care provider should any of these symptoms occur.

- **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
- **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.
- **Changes in body fat** can happen in some people who take HIV-1 medicines. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the main part of your body (trunk). Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known.
- **Changes in 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.

The most common side effects of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are:

- trouble concentrating
- headache
- not feeling well
- nasal signs and symptoms
- rash
- trouble sleeping
- depression
- cough
- abnormal dreams
- nausea
- tiredness
- diarrhea
- dizziness
- pain
- weakness

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 at 20° to 25°C (68° to 77°F).
- Keep efavirenz, lamivudine and tenofovir disoproxil fumarate tablets in the original container.

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 ingredients: efavirenz USP, lamivudine USP, and tenofovir disoproxil fumarate

Inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, lactose anhydrous, magnesium stearate, microcrystalline cellulose, pregelatinized starch, polyethylene glycol, polyvinyl alcohol, sodium lauryl sulfate, talc and titanium dioxide.

Brands listed are the trademarks of their respective owners and are not trademarks of Laurus Labs Limited or Laurus Generics Inc.

For more information, call Laurus Generics Inc. at 1-833-3-LAURUS (1-833-352-8787).

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

Manufactured for:
Laurus Generics Inc.
400 Connell Drive
Suite 5200
Berkeley Heights, NJ 07922

Manufactured by:
Laurus Labs Limited
Visakhapatnam-531011
India

Revised: 11/2019