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Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets
2044504

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 POM | Schedule: S2 | PP

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

See full prescribing information for complete boxed warning.

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

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

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, a combination of one non-nucleoside reverse transcriptase inhibitor (efavirenz) and two nucleo(t)side reverse transcriptase inhibitors (lamivudine and tenofovir disoproxil fumarate), are indicated for use alone as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients weighing at least 40 kg. (1)

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

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

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

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

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

- Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are contraindicated in patients with previous hypersensitivity (e.g., Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the components of this product. (4.1)

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

- Coadministration with Other Products: Do not use with other efavirenz, lamivudine or tenofovir-containing products or emtricitabine-containing products. Do not administer in combination with adefovir dipivoxil. (5.3)
- Hepatic decompensation, some fatal, has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy and interferon and ribavirin-based regimens. Monitor for treatment-associated toxicities. Discontinue efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, as medically appropriate and consider dose reduction or discontinuation of interferon alfa, ribavirin, or both. (5.4)
- Pancreatitis: Use with caution in pediatric patients with a history of pancreatitis or other significant risk factors for pancreatitis. Discontinue efavirenz, lamivudine and tenofovir disoproxil fumarate tablets as clinically appropriate. (5.5)
- New Onset or Worsening Renal Impairment: Can include acute renal failure and Fanconi syndrome. Assess estimated creatinine clearance before initiating treatment with tenofovir disoproxil fumarate, a component of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. In patients at risk for renal dysfunction, assess estimated creatinine clearance, serum phosphorus, urine glucose and urine protein before initiating treatment with tenofovir and periodically during treatment. Avoid administering efavirenz, lamivudine and tenofovir disoproxil fumarate tablets with concurrent or recent use of nephrotoxic drugs. (5.6)
- Serious Psychiatric Symptoms: Immediate medical evaluation is recommended for serious psychiatric symptoms such as severe depression or suicidal ideation. (5.7, 17)
- Nervous System Symptoms (NSS): NSS are frequent, usually begin 1 to 2 days after initiating therapy and resolve in 2 to 4 weeks. Dosing at bedtime may improve tolerability. NSS are not predictive of onset of psychiatric symptoms. (5.8, 17)
- Embryo-Fetal Toxicity: Avoid administration in the first trimester of pregnancy as fetal harm may occur. (5.9, 8.1)
- Hepatotoxicity: Monitor liver function tests before and during treatment in patients with underlying hepatic disease, including hepatitis B or C coinfection, marked transaminase elevations, or who are taking medications associated with liver toxicity. Among reported cases of hepatic failure, a few occurred in patients with no pre-existing hepatic disease. (5.11, 8.7)
- Rash: Rash usually begins within 1 to 2 weeks after initiating therapy and resolves within 4 weeks. Discontinue if severe rash develops. (5.10, 17)
- Convulsions: Use caution in patients with a history of seizures. (5.12)
- Lipids: Total cholesterol and triglyceride elevations. Monitor before therapy and periodically thereafter. (5.13)
- Decreases in Bone Mineral Density (BMD): Observed in HIV-infected patients. Consider assessment of BMD in patients with a history of pathologic fracture or other risk factors for osteoporosis or bone loss. (5.14)
- Immune Reconstitution Syndrome: Observed in HIV-infected patients. May necessitate further evaluation and treatment. (5.15)
- Redistribution/Accumulation of Body Fat: Observed in HIV-infected patients receiving antiretroviral combination therapy. (5.16)

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

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

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

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

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

- Pregnancy: Women should avoid pregnancy during efavirenz therapy, a component of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, and for 12 weeks after discontinuation. (5.9)
- Lactation: Breastfeeding not recommended. (8.2)
- Females and Males of Reproductive Potential: Pregnancy testing and contraception are recommended. (8.3)
- Hepatic Impairment: Efavirenz is not recommended for patients with moderate or severe hepatic impairment. Use caution in patients with mild hepatic impairment. (8.7)
- Pediatric Patients: The incidence of rash was higher than in adults. (5.10, 6.1, 8.4)

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

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FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT ACUTE EXACERBATIONS OF HEPATITIS B

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

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

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

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

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

2.2 Dose Adjustment for Renal Impairment

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

3 DOSAGE FORMS AND STRENGTHS

Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets are available containing 600 mg of efavirenz, USP, 300 mg of lamivudine, USP and 300 mg of tenofovir disoproxil fumarate equivalent to 245 mg of tenofovir disoproxil.

- The 600 mg/300 mg/300 mg tablets are yellow colored, capsule shaped, bevel edged biconvex film coated tablets debossed with 'I' on one side and '127' on the other side.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are contraindicated in patients with a previous hypersensitivity reaction to any of the components contained in the formulation.

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis/Severe Hepatomegaly With Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

5.2 Patients Coinfected with HIV-1 and HBV

It is recommended that all patients with HIV-1 be tested for the presence of chronic hepatitis B virus (HBV) before initiating antiretroviral therapy. Discontinuation of anti-HBV therapy, including lamivudine and tenofovir disoproxil fumarate, may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted.

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

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

5.3 Coadministration with Other Products

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

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should not be administered in combination with HEPSERA® (adefovir dipivoxil) *[see Drug Interactions (7.3)]*.

5.4 Use With Interferon- and Ribavirin-Based Regimens

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

5.5 Pancreatitis

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

5.6 New Onset or Worsening Renal Impairment

Tenofovir, a component of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets is principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir disoproxil fumarate *[see Adverse Reactions (6.2)]*.

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

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should be avoided with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs)) *[see Drug Interactions (7.3)]*. Cases of acute renal failure after initiation of high dose or multiple NSAIDs have been reported in HIV-infected patients with risk factors for renal dysfunction who appeared stable on tenofovir disoproxil fumarate. Some patients required hospitalization and renal replacement therapy. Alternatives to NSAIDs should be considered, if needed, in patients at risk for renal dysfunction.

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

5.7 Psychiatric Symptoms

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

There have also been occasional postmarketing reports of death by suicide, delusions, psychosis-like behavior, and catatonia, although a causal relationship to the use of efavirenz cannot be determined from these reports. Patients with serious psychiatric adverse experiences should seek immediate medical evaluation to assess the possibility that the symptoms may be related to the use of efavirenz, and if so, to determine whether the risks of continued therapy outweigh the benefits.

5.8 Nervous System Symptoms

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

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

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

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

5.9 Embryo-Fetal Toxicity

Efavirenz, a component of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, may cause fetal harm when administered during the first trimester to a pregnant woman. Advise females of reproductive potential who are receiving efavirenz to avoid pregnancy. *[See Use in Specific Populations (8.1).]*

5.10 Rash

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

Efavirenz can generally be reinitiated in patients interrupting therapy because of rash. Efavirenz should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement, or fever. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash. For patients who have had a life-threatening cutaneous reaction (e.g., Stephens-Johnson syndrome), alternate therapy should be considered *[see Contraindications (4.1)]*.

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

5.11 Hepatotoxicity

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

5.12 Convulsions

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

5.13 Lipid Elevations

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

5.14 Bone Effects

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

Clinical trials evaluating tenofovir disoproxil fumarate in pediatric and adolescent subjects were conducted. Under normal circumstances, BMD increases rapidly in pediatric patients. In HIV-1 infected subjects aged 2 years to less than 18 years, bone effects were similar to those observed in adult subjects and suggest increased bone turnover. Total body BMD gain was less in the tenofovir disoproxil fumarate-treated HIV-1 infected pediatric subjects as compared to the control groups. Similar trends were observed in chronic hepatitis B infected adolescent subjects aged 12 years to less than 18 years. In all pediatric trials, skeletal growth (height) appeared to be unaffected *[see Adverse Reactions (6.1)]*.

The effects of tenofovir disoproxil fumarate-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. Assessment of BMD should be considered for adults and pediatric patients 12 years of age and older who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained.

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

5.15 Immune Reconstitution Syndrome

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

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

5.16 Fat Redistribution

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

5.17 QTc Prolongation

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

6 ADVERSE REACTIONS

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

- Lactic Acidosis/Severe Hepatomegaly with Steatosis *[see Boxed Warning, Warnings and Precautions (5.1)]*.
- Exacerbations of Hepatitis B *[see Boxed Warning, Warnings and Precautions (5.2)]*.
- Hepatic Decompensation in Patients Co-infected with HIV-1 and Hepatitis C *[see Warnings and Precautions (5.4)]*.
- Pancreatitis *[see Warnings and Precautions (5.5)]*.
- New Onset or Worsening Renal Impairment *[see Warnings and Precautions (5.6)]*.
- Psychiatric Symptoms *[see Warnings and Precautions (5.7)]*.
- Nervous System Symptoms *[see Warnings and Precautions (5.8)]*.
- Rash *[see Warnings and Precautions (5.10)]*.
- Decreases in Bone Mineral Density *[see Warnings and Precautions (5.14)]*.
- Immune Reconstitution Syndrome *[see Warnings and Precautions (5.15)]*.
- Fat Redistribution *[see Warnings and Precautions (5.16)]*.

6.1 Clinical Trials Experience

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

Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate

Treatment-Naïve Patients

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

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

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

	Tenofovir Disoproxil Fumarate + 3TC + EFV	d4T + 3TC + EFV
	N=299	N=301
Body as a Whole		
Headache	14%	17%
Pain	13%	12%
Fever	8%	7%
Abdominal pain	7%	12%
Back pain	9%	8%
Asthenia	6%	7%
Digestive System		
Diarrhea	11%	13%
Nausea	8%	9%
Dyspepsia	4%	5%
Vomiting	5%	9%
Metabolic Disorders		
Lipodystrophy[b]	1%	8%
Musculoskeletal		
Arthralgia	5%	7%
Myalgia	3%	5%
Nervous System		
Depression	11%	10%
Insomnia	5%	8%
Dizziness	3%	6%
Peripheral neuropathy[c]	1%	5%
Anxiety	6%	6%
Respiratory		
Pneumonia	5%	5%
Skin and Appendages		
Rash event[d]	18%	12%

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

Laboratory Abnormalities: With the exception of fasting cholesterol and fasting triglyceride elevations that were more common in the stavudine group (40% and 9%) compared with tenofovir disoproxil fumarate (19% and 1%) respectively, laboratory abnormalities observed in this study occurred with similar frequency in the tenofovir disoproxil fumarate and stavudine treatment arms. A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 2.

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

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

Changes in Bone Mineral Density: In HIV-1 infected adult subjects in Study 903, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in subjects receiving tenofovir disoproxil fumarate + lamivudine + efavirenz (-2.2% ± 3.9) compared with subjects receiving stavudine + lamivudine + efavirenz (-1.0% ± 4.6) through 144 weeks. Changes in BMD at the hip were similar between the two treatment groups (-2.8% ± 3.5 in the tenofovir disoproxil fumarate group vs. -2.4% ± 4.5 in the stavudine group). In both groups, the majority of the reduction in BMD occurred in the first 24-48 weeks of the trial and this reduction was sustained through Week 144. Twenty-eight percent of tenofovir disoproxil fumarate-treated subjects vs. 21% of the stavudine-treated subjects lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 subjects in the tenofovir disoproxil fumarate group and 6 subjects in the stavudine group. In addition, there were significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C telopeptide, and urinary N telopeptide) and higher serum parathyroid hormone levels and 1,25 Vitamin D levels in the tenofovir disoproxil fumarate group relative to the stavudine group; however, except for bone-specific alkaline phosphatase, these changes resulted in values that remained within the normal range *[see Warnings and Precautions (5.14)]*.

Pediatrics

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

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

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

6.2 Postmarketing Experience

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

Efavirenz

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

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

Endocrine: gynecomastia.

Gastrointestinal: constipation, malabsorption.

Cardiovascular: flushing, palpitations.

Liver and Biliary System: hepatic enzyme increase, hepatic failure, hepatitis. A few of the postmarketing reports of hepatic failure, including cases in patients with no pre-existing hepatic disease or other identifiable risk factors, were characterized by a fulminant course, progressing in some cases to transplantation or death.

Metabolic and Nutritional: hypercholesterolemia, hypertriglyceridemia.

Musculoskeletal: arthralgia, myalgia, myopathy.

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

Respiratory: dyspnea.

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

Special Senses: abnormal vision, tinnitus.

Lamivudine

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

Endocrine and Metabolic: hyperglycemia.

General: weakness.

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

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

Hypersensitivity: anaphylaxis, urticaria.

Musculoskeletal: muscle weakness, CPK elevation, rhabdomyolysis.

Skin: Alopecia, pruritus.

Tenofovir Disoproxil Fumarate

Immune System Disorders: allergic reaction, including angioedema.

Metabolism and Nutrition Disorders: lactic acidosis, hypokalemia, hypophosphatemia.

Respiratory, Thoracic, and Mediastinal Disorders: dyspnea.

Gastrointestinal Disorders: pancreatitis, increased amylase, abdominal pain.

Renal and Urinary Disorders: renal insufficiency, Acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria *[see Warnings and Precautions (5.6)]*.

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

Skin and Subcutaneous Tissue Disorders: rash.

Musculoskeletal and Connective Tissue Disorders: rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy.

General Disorders and Administration Site Conditions: asthenia.

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

7 DRUG INTERACTIONS

7.1 Not Recommended with Other Antiretroviral Medications

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

7.2 QT Prolonging Drugs

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

7.3 Drugs Affecting Renal Function

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

7.4 Cannabinoid Test Interaction

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

7.5 Drug-Drug Interactions

Efavirenz has been shown *in vivo* to induce CYP3A and CYP2B6. Other compounds that are substrates of CYP3A or CYP2B6 may have decreased plasma concentrations when coadministered with efavirenz.

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

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

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

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

Concomitant Drug Class: Drug Name	Effect	Clinical Comment
Anticoagulant: Warfarin	↑ or ↓ warfarin	Monitor INR and adjust warfarin dosage if necessary.
Anticonvulsants: Carbamazepine	↓ carbamazepine* ↓ efavirenz*	There are insufficient data to make a dose recommendation for efavirenz. Alternative anticonvulsant treatment should be used.
Phenytoin Phenobarbital	↓ anticonvulsant ↓ efavirenz	Monitor anticonvulsant plasma levels periodically because of potential for reduction in anticonvulsant and/or efavirenz plasma levels.
Antidepressants: Bupropion	↓ bupropion*	Increases in bupropion dosage should be guided by clinical response. Bupropion dose should not exceed the maximum recommended dose.
Sertraline	↓ sertraline*	Increases in sertraline dosage should be guided by clinical response.
Antifungals: Itraconazole Ketoconazole	↓ itraconazole* ↓ hydroxyitraconazole* ↓ ketoconazole	Consider alternative antifungal treatment because no dose recommendation for itraconazole or ketoconazole can be made.
Posaconazole	↓ posaconazole*	Avoid concomitant use unless the benefit outweighs the risks.
Anti-infective: Clarithromycin	↓ clarithromycin* ↑ 14-OH metabolite*	Consider alternatives to macrolide antibiotics because of the risk of QT interval prolongation.
Antimycobacterial: Rifabutin	↓ rifabutin*	Increase daily dose of rifabutin by 50%. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week.
Antimalarials: Artemether/lumefantrine	↓ artemether* ↓ dihydroartemisinin* ↓ lumefantrine*	Consider alternatives to artemether/lumefantrine because of the risk of QT interval prolongation.
Atovaquone/ proguanil	↓ atovaquone ↓ proguanil	Concomitant administration is not recommended.
Calcium channel blockers: Diltiazem	↓ diltiazem* ↓ desacetyl diltiazem* ↓ N-monodesmethyldiltiazem*	Diltiazem dose adjustments should be guided by clinical response (refer to the full prescribing information for diltiazem).
Others (e.g., felodipine, nicardipine, nifedipine, verapamil)	↓ calcium channel blocker	When coadministered with efavirenz, dosage adjustment of calcium channels blocker may be needed and should be guided by clinical response (refer to the full prescribing information for the calcium channel blocker).
HMG-CoA reductase inhibitors: Atorvastatin Pravastatin Simvastatin	↓ atorvastatin* ↓ pravastatin* ↓ simvastatin*	Plasma concentrations of atorvastatin, pravastatin, and simvastatin decreased. Consult the full prescribing information for the HMG-CoA reductase inhibitor for guidance on individualizing the dose.
Hepatitis C antiviral agents: Boceprevir	↓ boceprevir*	Concomitant administration of boceprevir is not recommended.
Simeprevir	↓ simeprevir* ↔ efavirenz	Concomitant administration of simeprevir is not recommended.
Ledipasvir/Sofosbuvir	↑ tenofovir disoproxil fumarate	Monitor for adverse reactions associated with tenofovir disoproxil fumarate.
Hepatitis B antiviral agents Adefovir dipivoxil		Concomitant administration of adefovir dipivoxil is not recommended.
Hormonal contraceptives: Oral Ethinyl estradiol/ Norgestimate		A reliable method of barrier contraception should be used in addition to hormonal contraceptives.
Implant Etonogestrel	↓ active metabolites of norgestimate*	A reliable method of barrier contraception should be used in addition to hormonal contraceptives. The interaction between etonogestrel and efavirenz has not been studied. Decreased exposure of etonogestrel may be expected. There have been postmarketing reports of contraceptive failure with etonogestrel in efavirenz-exposed patients.
	↓ etonogestrel	
Immunosuppressants: Cyclosporine, tacrolimus, sirolimus, and others metabolized by CYP3A	↓ immunosuppressant	Dose adjustments of the immunosuppressant may be required. Close monitoring of immunosuppressant concentrations for at least 2 weeks (until stable concentrations are reached) is recommended when starting or stopping treatment with efavirenz.
Narcotic analgesic: Methadone	↓ methadone*	Monitor for signs of methadone withdrawal and increase methadone dose if required to alleviate withdrawal symptoms.

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

7.6 Drugs without Clinically Significant Interactions

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Efavirenz:

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

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

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

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

Lamivudine:

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

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

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

Lamivudine pharmacokinetics in pregnant women were similar to those seen in non-pregnant adults and in postpartum women. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples. In a subset of subjects, amniotic fluid specimens were collected following natural rupture of membranes and confirmed that lamivudine crosses the placenta in humans. Amniotic fluid concentrations of lamivudine were typically 2 times greater than maternal serum levels and ranged from 1.2 to 2.5 mcg per mL (150 mg twice daily) and 2.1 to 5.2 mcg per mL (300 mg twice daily).

Animal Data: Studies in pregnant rats showed that lamivudine is transferred to the fetus through the placenta. Reproduction studies with orally administered lamivudine have been performed in rats and rabbits at doses producing plasma levels up to approximately 35 times that for the recommended adult HIV dose. No evidence of teratogenicity due to lamivudine was observed. Evidence of embryo-lethality was seen in the rabbit at exposure levels similar to those observed in humans but there was no indication of this effect in the rat at exposure levels up to 35 times those in humans.

Tenofovir Disoproxil Fumarate:

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

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

8.2 Lactation

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. Because of the potential for HIV-1 transmission in breastfed infants, advise women not to breastfeed.

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

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

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

8.3 Females and Males of Reproductive Potential

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

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

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

8.4 Pediatric Use

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

8.5 Geriatric Use

Clinical studies of efavirenz, lamivudine and tenofovir disoproxil fumarate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration of lamivudine in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Patients with Impaired Renal Function

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

8.7 Hepatic Impairment

Efavirenz, a component of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, is not recommended for patients with moderate or severe hepatic impairment because there are insufficient data to determine whether dose adjustment is necessary. Patients with mild hepatic impairment may be treated with efavirenz without any adjustment in dose. Because of the extensive cytochrome P450-mediated metabolism of efavirenz and limited clinical experience in patients with hepatic impairment, caution should be exercised in administering efavirenz to these patients *[see Warnings and Precautions (5.11)* and *Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

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

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

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

Lamivudine: There is no known specific treatment for overdose with lamivudine. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required because a negligible amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event.

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

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

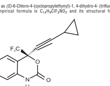
11 DESCRIPTION

Efavirenz, Lamivudine, and Tenofovir disoproxil fumarate Tablets are for oral administration. Each film coated tablet contains 600 mg of Efavirenz USP, 300 mg of Lamivudine USP, and 300 mg of Tenofovir disoproxil fumarate (equivalent to 245 mg of tenofovir disoproxil). In addition, each tablet contains the following inactive ingredients: Anhydrous lactose, croscarmellose sodium, hydroxy propyl cellulose, isopropyl alcohol, magnesium stearate, microcrystalline cellulose, Pregelatinized starch, sodium Lauryl sulfate and sodium starch glycolate. The tablets are coated with opadry II yellow which contains polyethylene glycol, poly vinyl alcohol, talc, titanium dioxide and iron oxide yellow.

Efavirenz

Efavirenz USP is a non-nucleoside reverse transcriptase inhibitor indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 infection.

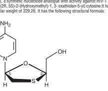
Efavirenz USP is chemically described as *(S)*-6-Chloro-4-(cyclopropylethynyl)-1, 4-dihydro-4- (trifluoromethyl)-2h-3, 1-Benzoxazin-2-one; Its empirical formula is $C_{14}H_9ClF_3NO_2$ and its structural formula is:



Efavirenz USP is white to slightly pink crystalline powder with a molecular mass of 315.68. It is soluble in methanol, practically insoluble in water.

Lamivudine

Lamivudine USP (also known as 3TC), a synthetic nucleoside analogue with activity against HIV-1 and HBV. The chemical name of lamivudine is (-)-1-[(2R, 5S)-2-(Hydroxymethyl)-1, 3- oxathiolan-5-yl] cytosine.It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.26. It has the following structural formula:



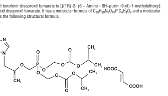
Lamivudine USP is an off – white solid. It is soluble in water.

Tenofovir disoproxil fumarate

Tenofovir disoproxil fumarate is a nucleotide analog HIV-1 reverse transcriptase inhibitor and an HBV reverse transcriptase inhibitor. Tenofovir disoproxil fumarate is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients 2 years of age and older.

Tenofovir disoproxil fumarate is indicated for the treatment of chronic hepatitis B in adults.

The chemical name of tenofovir disoproxil fumarate is [[(1R)-2- (6 – Amino - 9H–purin -9-yl)-1-methylethoxy] methyl] phosphonic acid disoproxil fumarate. It has a molecular formula of $C_{19}H_{30}N_5O_{10}P.C_4H_4O_4$ and a molecular weight of 635.5. It has the following structural formula.



Tenofovir disoproxil fumarate is a white crystalline powder which is sparingly soluble in methanol and in ethanol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are a fixed-dose combination of antiviral drugs efavirenz, lamivudine and tenofovir disoproxil fumarate with antiviral activity against HIV-1 *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

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

Efavirenz: In HIV-1 infected subjects time-to-peak plasma concentrations were approximately 3 to 5 hours and steady-state plasma concentrations were reached in 6 to 10 days. In 35 HIV-1 infected subjects receiving efavirenz 600 mg once daily, steady-state C_{max} was 12.9 ± 3.7 μM (mean ± SD), C_{min} was 5.6 ± 3.2 μM and AUC was 184 ± 73 μM·hr. Efavirenz is highly bound (approximately 99.5 to 99.75%) to human plasma proteins, predominantly albumin. Following administration of ^{14}C-labeled efavirenz, 14 to 34% of the dose was recovered in the urine (mostly as metabolites) and 16 to 61% was recovered in feces (mostly as parent drug). *In vitro* studies suggest CYP3A and CYP2B6 are the major isozymes responsible for efavirenz metabolism. Efavirenz has been shown to induce CYP enzymes, resulting in induction of its own metabolism. Efavirenz has a terminal half-life of 52 to 76 hours after single doses and 40 to 55 hours after multiple doses.

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

Tenofovir Disoproxil Fumarate: Following oral administration of a single 300 mg dose of tenofovir disoproxil fumarate to HIV-1 infected subjects in the fasted state, maximum serum concentrations (C_{max}) were achieved in 1.0 ± 0.4 hrs (mean ± SD) and C_{max} and AUC values were 296 ± 90 ng/mL and 2287 ± 685 ng•hr/mL, respectively. The oral bioavailability of tenofovir from tenofovir disoproxil fumarate in fasted subjects is approximately 25%. Less than 0.7% of tenofovir binds to human plasma proteins *in vitro* and the binding is independent of concentration over the range of 0.01 to 25 mcg/mL. Approximately 70 to 80% of the intravenous dose of tenofovir is recovered as unchanged drug in the urine. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion with a renal clearance in adults with normal renal function of 243 ± 33 mL/min (mean ± SD). Following a single oral dose, the terminal elimination half-life of tenofovir is approximately 17 hours.

Special Populations: *Race:* Efavirenz and Lamivudine: There are no significant or clinically relevant racial differences in efavirenz and lamivudine pharmacokinetics.

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

Gender: There are no significant or clinically relevant gender differences in the pharmacokinetics of efavirenz, lamivudine, and tenofovir disoproxil fumarate.

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

Pediatrics: This combination tablet should not be administered to patients weighing less than 40 kg.

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

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

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

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

Tenofovir Disoproxil Fumarate: The pharmacokinetics of tenofovir following a 300 mg single dose of tenofovir disoproxil fumarate have been studied in non-HIV infected subjects with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in subjects with hepatic impairment compared with unimpaired subjects. No change in tenofovir disoproxil fumarate dosing is required in patients with hepatic impairment.

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

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

Drug interaction studies were performed with efavirenz and other drugs likely to be coadministered or drugs commonly used as probes for pharmacokinetic interaction. The effects of coadministration of efavirenz on the C_{max}, AUC, and C_{min} are summarized in Table 4 (effect of efavirenz on other drugs) and Table 5 (effect of other drugs on efavirenz). For information regarding clinical recommendations see *Drug Interactions (7.5)*.

Table 4. 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-↑ 8%)	↓ 19% (11-25%)	↓ 44% (26-58%)
Simeprevir	150 mg qd x 14 days	600 mg qd x 14 days	23	↓ 51% (↓ 46-↓ 56%)	↓ 71% (↓ 67-↓ 74%)	↓ 91% (↓ 88-↓ 92%)
Azithromycin	600 mg single dose	400 mg qd x 7 days	14	↑ 22% (4-42%)	↔	NA
Clarithromycin	500 mg q12h x 7 days	400 mg qd x 7 days	11	↓ 26% (15-35%)	↓ 39% (30-46%)	↓ 53% (42-63%)
14-OH metabolite				↑ 49% (32-69%)	↑ 34% (18-53%)	↑ 26% (9-45%)
Fluconazole	200 mg x 7 days	400 mg qd x 7 days	10	↔	↔	↔
Itraconazole	200 mg q12h x 28 days	600 mg qd x 14 days	18	↓ 37% (20-51%)	↓ 39% (21-53%)	↓ 44% (27-58%)
Hydroxy-itraconazole				↓ 35% (12-52%)	↓ 37% (14-55%)	↓ 43% (18-60%)
Posaconazole	400 mg (oral suspension) bid x 10 and 20 days	400 mg qd x 10 and 20 days	11	↓ 45% (34-53%)	↓ 50% (40-57%)	NA
Rifabutin	300 mg qd x 14 days	600 mg qd x 14 days	9	↓ 32% (15-46%)	↓ 38% (28-47%)	↓ 45% (31-56%)
Voriconazole	400 mg po q12h x 1 day, then 200 mg po q12h x 8 days	400 mg qd x 9 days	NA	↓ 61%[a]	↓ 77%[a]	NA
	300 mg po q12h days 2-7	300 mg qd x 7 days	NA	↓ 36%[b] (21-49%)	↓ 55%[b] (45-62%)	NA
	400 mg po q12h days 2-7	300 mg qd x 7 days	NA	↑ 23%[b] (↓ 1-↑ 53%)	↓ 7%[b] (↓23-↑13%)	NA
Artemether/ lumefantrine	Artemether 20 mg/ lumefantrine 120 mg tablets (6 4-tablet doses over 3 days)	600 mg qd x 26 days	12			
Artemether				↓ 21%	↓ 51%	NA
dihydroartemisinin				↓ 38%	↓ 46%	NA
lumefantrine				↔	↓ 21%	NA
Atorvastatin	10 mg qd x 4 days	600 mg qd x 15 days	14	↓ 14% (1-26%)	↓ 43% (34-50%)	↓ 69% (49-81%)
Total active (including metabolites)				↓ 15% (2-26%)	↓ 32% (21-41%)	↓ 48% (23-64%)
Pravastatin	40 mg qd x 4 days	600 mg qd x 15 days	13	↓ 32% (↓ 59-↑ 12%)	↓ 44% (26-57%)	↓ 19% (0-35%)
Simvastatin	40 mg qd x 4 days	600 mg qd x 15 days	14	↓ 72% (63-79%)	↓ 68% (62-73%)	↓ 45% (20-62%)
Total active (including metabolites)				↓ 68% (55-78%)	↓ 60% (52-68%)	NA[c]
Carbamazepine	200 mg qd x 3 days, 200 mg bid x 3 days, then 400 mg qd x 29 days	600 mg qd x 14 days	12	↓ 20% (15-24%)	↓ 27% (20-33%)	↓ 35% (24-44%)
Epoxide metabolite				↔	↔	↓ 13% (↓ 30-↑7%)
Cetirizine	10 mg single dose	600 mg qd x 10 days	11	↓ 24% (18-30%)	↔	NA
Diltiazem	240 mg x 21 days	600 mg qd x 14 days	13	↓ 60% (50-68%)	↓ 69% (55-79%)	↓ 63% (44-75%)
Desacetyl diltiazem				↓ 64% (57-69%)	↓ 75% (59-84%)	↓ 62% (44-75%)
N-monodes-methyl diltiazem				↓ 28% (7-44%)	↓ 37% (17-52%)	↓ 37% (17-52%)
Ethinyl estradiol/ Norgestimate	0.035 mg/ 0.25 mg x 14 days	600 mg qd x 14 days				
Ethinyl estradiol			21	↔	↔	↔
Norelgestromine			21	↓ 46% (39-52%)	↓ 64% (62-67%)	↓ 82% (79-85%)
Levonorgestrel			6	↓ 80% (77-83%)	↓ 83% (79-87%)	↓ 86% (80-90%)
Lorazepam	2 mg single dose	600 mg qd x 10 days	12	↑ 16% (2-32%)	↔	NA
Methadone	Stable maintenance 35-100 mg daily	600 mg qd x 14-21 days	11	↓ 45% (25-59%)	↓ 52% (33-66%)	NA
Bupropion	150 mg single dose (sustained-release)	600 mg qd x 14 days	13	↓ 34% (21-47%)	↓ 55% (48-62%)	NA
Hydroxy-bupropion				↑ 50% (20-80%)	↔	NA
Paroxetine	20 mg qd x 14 days	600 mg qd x 14 days	16	↔	↔	↔
Sertraline	50 mg qd x 14 days	600 mg qd x 14 days	13	↓ 29% (15-40%)	↓ 39% (27-50%)	↓ 46% (31-58%)

↑ Indicates increase ↓ Indicates decrease ↔ Indicates no change or a mean increase or decrease of < 10%.
[a] 90% CI not available.
[b] Relative to steady-state administration of voriconazole (400 mg for 1 day, then 200 mg po q12h for 2 days).
[c] Not available because of insufficient data.
NA = not available.

Table 5. 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% (2-20%)	↑ 20% (15-26%)	NA
Simeprevir	150 mg qd x 14 days	600 mg qd x 14 days	23	↔	↓ 10% (5-15%)	↓ 13% (7-19%)
Azithromycin	600 mg single dose	400 mg qd x 7 days	14	↔	↔	↔
Clarithromycin	500 mg q12h x 7 days	400 mg qd x 7 days	12	↑ 11% (3-19%)	↔	↔
Fluconazole	200 mg x 7 days	400 mg qd x 7 days	10	↔	↑ 16% (6-26%)	↑ 22% (5-41%)
Itraconazole	200 mg q12h x 14 days	600 mg qd x 28 days	16	↔	↔	↔
Rifabutin	300 mg qd x 14 days	600 mg qd x 14 days	11	↔	↔	↓ 12% (↓ 24-↑1%)
Rifampin	600 mg x 7 days	600 mg qd x 7 days	12	↓ 20% (11-28%)	↓ 26% (15-36%)	↓ 32% (15-46%)
Voriconazole	400 mg po q12h x 1 day, then 200 mg po q12h x 8 days	400 mg qd x 9 days	NA	↑ 38%[a]	↑ 44%[a]	NA
	300 mg po q12h days 2-7	300 mg qd x 7 days	NA	↓ 14%[b] (7-21%)	↔[b]	NA
	400 mg po q12h days 2-7	300 mg qd x 7 days	NA	↔[b]	↑ 17%[b] (6-29%)	NA
Artemether/ Lumefantrine	Artemether 20 mg/ lumefantrine 120 mg tablets (6 4-tablet doses over 3 days)	600 mg qd x 26 days	12	↔	↓ 17%	NA
Atorvastatin	10 mg qd x 4 days	600 mg qd x 15 days	14	↔	↔	↔
Pravastatin	40 mg qd x 4 days	600 mg qd x 15 days	11	↔	↔	↔
Simvastatin	40 mg qd x 4 days	600 mg qd x 15 days	14	↓ 12% (↓ 28- ↑8%)	↔	↓ 12% (↓ 25- ↑3%)
Aluminum hydroxide 400 mg, magnesium hydroxide 400 mg, plus simethicone 40 mg	30 mL single dose	400 mg single dose	17	↔	↔	NA
Carbamazepine	200 mg qd x 3 days, 200 mg bid x 3 days, then 400 mg qd x 15 days	600 mg qd x 35 days	14	↓ 21% (15-26%)	↓ 36% (32-40%)	↓ 47% (41-53%)
Cetirizine	10 mg single dose	600 mg qd x 10 days	11	↔	↔	↔
Diltiazem	240 mg x 14 days	600 mg qd x 28 days	12	↑ 16% (6-26%)	↑ 11% (5-18%)	↑ 13% (1-26%)
Famotidine	40 mg single dose	400 mg single dose	17	↔	↔	NA
Paroxetine	20 mg qd x 14 days	600 mg qd x 14 days	12	↔	↔	↔
Sertraline	50 mg qd x 14 days	600 mg qd x 14 days	13	↑ 11% (6-16%)	↔	↔

↑ Indicates increase ↓ Indicates decrease ↔ Indicates no change or a mean increase or decrease of < 10%.
[a] 90% CI not available.
[b] Relative to steady-state administration of efavirenz (600 mg once daily for 9 days).
NA = not available.

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

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

Coadministration of TMP/SMX (160 mg/ 800 mg) with lamivudine 300 mg single dose (n = 14 HIV-1 patients) resulted in an increase of 43% ± 23% (mean ± SD) in lamivudine AUC_∞, a decrease of 29% ± 13% in lamivudine oral clearance, and a decrease of 30% ± 36% in lamivudine renal clearance. The pharmacokinetic properties of TMP and SMX were not altered by coadministration with lamivudine. There is no information regarding the effect on lamivudine pharmacokinetics of higher doses of TMP/SMX such as those used in treat PCP.

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

Table 6 summarizes pharmacokinetic effects of coadministered drug on tenofovir pharmacokinetics. No clinically significant drug interactions have been observed between tenofovir and methadone, oral contraceptives, or ribavirin.

Table 6. Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir[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 Sofosbuvir[c]	90/400 once daily x 14 days	15	↑ 79 (↑ 56 to ↑ 104)	↑ 98 (↑ 77 to ↑ 123)	↑ 163 (↑ 132 to ↑ 197)
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.

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

12.4 Microbiology

Mechanism of Action

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

Lamivudine: Lamivudine is a synthetic nucleoside analogue with activity against HIV-1 and HBV. Intracellularly, lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is inhibition of HIV-1 reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue.

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

Antiviral Activity

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

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

Tenofovir Disoproxil Fumarate: The antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The EC_{50} (50% effective concentration) values for tenofovir were in the range of 0.04 μM to 8.5 μM. In drug combination studies, tenofovir was not antagonistic with nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir). Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC_{50} values ranged from 0.5 μM to 2.2 μM) and strain specific activity against HIV-2 (EC_{50} values ranged from 1.6 μM to 5.5 μM). Please see the full prescribing information for VIREAD for information regarding the inhibitory activity of lamivudine against HBV.

Resistance

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

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

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

Cross-Resistance

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

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

Tenofovir Disoproxil Fumarate: Cross-resistance among NRTIs has been observed. The K65R and K70 E substitutions selected by tenofovir are also selected in some HIV-1 infected subjects treated with abacavir or didanosine. HIV-1 isolates with the K65R substitution also showed reduced susceptibility to emtricitabine and lamivudine. HIV-1 isolates from subjects (N = 20) whose HIV-1 expressed a mean of 3 zidovudine-associated RT amino acid substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N) showed a 3.1-fold decrease in the susceptibility to tenofovir. Subjects whose virus expressed an L74V substitution without zidovudine resistance-associated substitutions (N = 8) had reduced response to VIREAD. Limited data are available for patients whose virus expressed a Y115F substitution (N = 3), Q151M substitution (N = 2), or T69 insertion (N = 4), all of whom had a reduced response.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Efavirenz tested negative in a battery of *in vitro* and *in vivo* genotoxicity assays. These included bacterial mutation assays in *S. typhimurium* and *E. coli*, mammalian mutation assays in Chinese hamster ovary cells, chromosome aberration assays in human peripheral blood lymphocytes or Chinese hamster ovary cells, and an *in vivo* mouse bone marrow micronucleus assay.

Efavirenz did not impair mating or fertility of male or female rats, and did not affect sperm of treated male rats. The reproductive performance of offspring born to female rats given efavirenz was not affected. The AUCs at the NOAEL values in male (200 mg/kg) and female (100 mg/kg) rats were approximately ≤ 0.15 times that in humans at the recommended clinical dose

Lamivudine: Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) the human exposures at the recommended dose of 300 mg. Lamivudine was not mutagenic in a microbial mutagenicity assay, in an *in vitro* cell transformation assay, in a rat micronucleus test, in a rat bone marrow cytogenetic assay, and in assay for unscheduled DNA synthesis in rat liver. Lamivudine showed no evidence of *in vivo* genotoxic activity in the rat at oral doses of up to 2000 mg per kg, producing plasma levels of 35 to 45 times those in humans at the recommended dose for HIV-1 infection. In a study of reproductive performance, lamivudine administered to rats at doses up to 4,000 mg per kg per day, producing plasma levels 47 to 70 times those in humans, revealed no evidence of impaired fertility and no effect on the survival, growth, and development to weaning of the offspring.

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

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

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

13.2 Animal Toxicology and/or Pharmacology

Efavirenz: Nonsustained convulsions were observed in 6 of 20 monkeys receiving efavirenz at doses yielding plasma AUC values 4- to 13-fold greater than those in humans given the recommended dose *[see Warnings and Precautions (5.12)]*.

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

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

14 CLINICAL STUDIES

14.1 Clinical Efficacy in Patients with HIV-1 Infection

Treatment-Naïve Adult Patients

Study 903

Data through 144 weeks are reported for Study 903, a double-blind, active-controlled multicenter study comparing tenofovir disoproxil fumarate (300 mg once daily) administered in combination with lamivudine and efavirenz versus stavudine (d4T), lamivudine, and efavirenz in 600 antiretroviral-naïve subjects. Subjects had a mean age of 36 years (range 18 to 64), 74% were male, 64% were Caucasian and 20% were Black. The mean baseline CD4+ cell count was 279 cells/mm³ (range 3 to 956) and median baseline plasma HIV-1 RNA was 77,600 copies/mL (range 417 to 5,130,000). Subjects were stratified by baseline HIV-1 RNA and CD4+ cell count. Forty-three percent of subjects had baseline viral loads >100,000 copies/mL and 39% had CD4+ cell counts <200 cells/mm³. Treatment outcomes through 48 and 144 weeks are presented in Table 7.

Table 7 Outcomes of Randomized Treatment at Week 48 and 144 (Study 903)

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

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

Achievement of plasma HIV-1 RNA concentrations of less than 400 copies/mL at Week 144 was similar between the two treatment groups for the population stratified at baseline on the basis of HIV-1 RNA concentration (> or ≤100,000 copies/mL) and CD4+ cell count (< or ≥200 cells/mm³). Through 144 weeks of therapy, 62% and 58% of subjects in the tenofovir disoproxil fumarate and stavudine arms, respectively achieved and maintained confirmed HIV-1 RNA <50 copies/mL. The mean increase from baseline in CD4+ cell count was 263 cells/mm³ for the tenofovir disoproxil fumarate arm and 283 cells/mm³ for the stavudine arm. Through 144 weeks, 11 subjects in the tenofovir disoproxil fumarate group and 9 subjects in the stavudine group experienced a new CDC Class C event.

16 HOW SUPPLIED/STORAGE AND HANDLING

Efavirenz, Lamivudine, and Tenofovir disoproxil fumarate tablets 600 mg/300 mg/300 mg are Yellow colored, capsule shaped, bevel edged biconvex film coated tablets debossed with 'I' on one side and '127' on the other side. They are supplied as follows:

Bottles of 30 tablets (NDC 68554-3077-0)
Bottles of 90 tablets (NDC 68554-3077-1)
Bottles of 100 tablets (NDC 68554-3077-2)

Store below 30°C.

Dispense in original container with attached prescribing information that contains the Patient Information Leaflet.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

Information for Patients

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

- may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription, nonprescription medication, or herbal products, particularly St. John's wort.
- are not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician when using efavirenz, lamivudine and tenofovir disoproxil fumarate tablets.
- Patients should avoid doing things that can spread HIV-1 infection to others.
  - **Do not share or reuse needles or other injection equipment.**
  - **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
  - **Do not have any kind of sex without protection. Always practice safer sex by** using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.
  - **Do not breastfeed.** Lamivudine and tenofovir are excreted in breast milk. Mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

Also:

- The long term effects of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are unknown.
- Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are for oral ingestion only.
- Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should not be discontinued without first informing their physician.
- It is important to take efavirenz, lamivudine and tenofovir disoproxil fumarate tablets on a regular dosing schedule and to avoid missing doses.
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Treatment with efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should be suspended in any patient who develops clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity (including nausea, vomiting, unusual or unexpected stomach discomfort, and weakness) *[see Warnings and Precautions (5.1)]*.
- Patients with HIV-1 should be tested for Hepatitis B virus (HBV) before initiating antiretroviral therapy.
- Severe acute exacerbations of hepatitis have been reported in patients who are infected with HBV or coinfected with HBV and HIV-1 and have discontinued lamivudine and tenofovir disoproxil fumarate, components of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets *[see Warnings and Precautions (5.2)]*.
- Patients with HIV-1/HCV co-infection should be informed that hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin *[see Warnings and Precautions (5.4)]*.
- In patients with chronic hepatitis B, it is important to obtain HIV antibody testing prior to initiating lamivudine and tenofovir disoproxil fumarate, components of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets.
- Renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported. Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should be avoided with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple NSAIDs) and are not recommended for patients with impaired renal function (i.e., creatinine clearance less than 50 mL/min) or patients with end-stage renal disease (ESRD) requiring hemodialysis *[see Dosage and Administration (2.2)]*.
- Patients should be informed that central nervous system symptoms (NSS) including dizziness, insomnia, impaired concentration, drowsiness, and abnormal dreams are commonly reported during the first weeks of therapy with efavirenz, a component of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets *[see Warnings and Precautions (5.8)]*. Dosing at bedtime may improve the tolerability of these symptoms, which are likely to improve with continued therapy. Patients should be alerted to the potential for additive effects when used concomitantly with alcohol or psychoactive drugs. Patients should be instructed that if they experience NSS they should avoid potentially hazardous tasks such as driving or operating machinery.
- Patients should be informed that serious psychiatric symptoms including severe depression, suicide attempts, aggressive behavior, delusions, paranoia, psychosis-like symptoms and catatonia have been reported in patients receiving efavirenz *[see Warnings and Precautions (5.7)]*. If they experience severe psychiatric adverse experiences they should seek immediate medical evaluation. Patients should be advised to inform their physician of any history of mental illness or substance abuse.
- Patients should be informed that a common side effect of efavirenz is rash *[see Warnings and Precautions (5.10)]*. Rashes usually go away without any change in treatment. However, since rash may be serious, patients should be advised to contact their physician promptly if rash occurs.
- Advise females of reproductive potential to use effective contraception as well as a barrier method during treatment with efavirenz, lamivudine and tenofovir disoproxil fumarate tablets and for 12 weeks after discontinuation of efavirenz. Advise patients to contact their healthcare provider if they plan to become pregnant, become pregnant, or if pregnancy is suspected during treatment with efavirenz, lamivudine and tenofovir disoproxil fumarate tablets.
- Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should not be administered in combination with HEPSERA® (adefovir dipivoxil) *[see Warnings and Precautions (5.3)]*.
- Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should not be coadministered with other efavirenz-containing, lamivudine-containing, tenofovir disoproxil fumarate-containing, or emtricitabine-containing drugs, including COMBIVIR® (lamivudine/zidovudine), EPIVIR® or EPIVIR-HBV® (lamivudine), EPZICOM® (abacavir sulfate/lamivudine), or TRIZIVIR® (abacavir sulfate/lamivudine/zidovudine), EMTRIVA® (emtricitabine), STRIBILD® (elvitegravir/cobicistat/tenofgvir/emtricitabine), ATRIPLA® (emtricitabine/efavirenz/tenofovir disoproxil fumarate), or TRUVADA® (emtricitabine/tenofovir disoproxil fumarate) *[see Warnings and Precautions (5.3)]*.
- Decreases in bone mineral density have been observed with the use of lamivudine and tenofovir disoproxil fumarate, components of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, in patients with HIV. Bone mineral density monitoring should be considered in patients who have a history of pathologic bone fracture or at risk for osteopenia *[see Warnings and Precautions (5.14)]*.
- Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy, including efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, and that the cause and long-term health effects of these conditions are not known at this time *[see Warnings and Precautions (5.16)]*.
- In some patients with advanced HIV infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. Advise patients to inform their healthcare provider immediately of any symptoms of infection *[see Warnings and Precautions (5.15)]*.

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Manufactured by:
HETERO LABS LIMITED
Unit-III, 22-110, I.D.A., Jeedimetla,
Hyderabad-500 055, Telangana, India.

Revised: June 2017

Size : 500 x 950 mm
Book Folding : 45 x 60 mm
Color : Black
Spec: Printed on 40 GSM Bible paper, front & back side printing.

Pharma Code : 5377 5378

Note: Pharma code position, Orientation & Product Name Size are tentative, will be change based on folding size

DESTAQUES DAS INFORMAÇÕES DE PRESCRIÇÃO

Esses destaques não incluem todas as informações necessárias para usar o EFAVIRENZ, LAMIVUDINE E TENOFOVIR DISOPROXIL FUMARATE em comprimidos de forma segura e eficaz. Veja todas as informações completas de prescrição para os comprimidos de EFAVIRENZ, LAMIVUDINA E TENOFOVIR DISOPROXIL FUMARATO.

Comprimidos de EFAVIRENZ, LAMIVUDINA e TENOFOVIR DISOPROXIL FUMARATO para uso oral

POM | Schedule: S2 | PP

ATENÇÃO: ACIDOSE LÁCTICA/HEPATOMEGALIA GRAVE COM ESTEATOSE e EXACERAÇÕES AGUDAS DA HEPATITE B PÓS-TRATAMENTO

Veja toda a informação prescrita na bula.

• Acidose lática e hepatomegalia com esteatose, incluindo casos fatais, tem sido relatados com o uso de análogos de nucleósidos, incluindo lamivudina e tenofovir disoproxil fumarato. (5.1)

• Foram identificadas exacerbações agudas graves da hepatite B em pacientes coinfectados com vírus da hepatite B (VHB) e vírus da imunodeficiência humana (HIV-1) e pararam a lamivudina e o fumarato de tenofovir disoproxil. Monitorize a função hepatica de perto nesses pacientes e, se apropriado, inicie o tratamento anti hepatite B. (5.2)

INDICAÇÕES E USO

Os comprimidos de efavirenz, lamivudina e tenofovir disoproxil fumarato, uma combinação de um inibidor de transcriptase reversa não nucleósido (efavirenz) e dois inibidores laterais da transcriptase reversa (lamivudina e tenofovir disoproxil fumarato), são indicados para uso sozinho como um regime completo para o tratamento da infecção pelo vírus da imunodeficiência humana tipo 1 (HIV-1) em adultos e pacientes pediátricos pesando, pelo menos, 40 kg. (1)

DOSAGEM E ADMINISTRAÇÃO

• Dose sugerida: um comprimido (contendo 600 mg de efavirenz, 300 mg de lamivudina e 300 mg de fumarato de tenofovir disoproxil) administrado uma vez ao dia, por via oral, em jejum, de preferência na hora de dormir. (2.1)

DOSAGEM

Comprimidos: 600 mg de efavirenz, 300 mg de lamivudina e 300 mg de fumarato de tenofovir disoproxil. (3)

CONTRAINDICAÇÕES

• Os comprimidos de efavirenz, lamivudina e tenofovir disoproxil fumarato estão contraindicados a pacientes com hipersensibilidade prévia (por exemplo, síndrome de Stevens-Johnson, eritema multiforme ou erupções cutâneas tóxicas) a qualquer dos componentes deste produto. (4.1)

AVISOS E PRECAUÇÕES

- Coadministração com outros produtos: não use com outros produtos que contenham efavirenz, lamivudina, tenofovir ou produtos que contenham emtricitabina. Não administrar juntamente com adefovir dipivoxil. (5.3)
- Alguma descompensação hepática, alguma fatal, ocorreu em pacientes coinfectados com HIV-1/HCV que receberam terapia antiretroviral combinada e regimes baseados em interferão e baseados em ribavirina. Monitorar toxicidades ligadas ao tratamento. Descontinue os comprimidos de efavirenz, lamivudina e tenofovir disoproxil fumarato, como medicamente apropriado e considere a redução da dose ou a descontinuação do interferão alfa, ribavirina ou ambos. (5.4)
- Pancreatite: use com cuidado em pacientes pediátricos com histórico de pancreatite ou outros fatores de risco significativos para pancreatite. Descontinue os comprimidos de efavirenz, lamivudina e tenofovir disoproxil fumarato como clinicamente apropriado. (5.5)
- Novo Início ou Piora da Insuficiência Renal: pode incluir insuficiência renal aguda e síndrome de Fanconi. Avalie a depuração estimada da creatinina antes de iniciar o tratamento com tenofovir disoproxil fumarato, um componente dos comprimidos de efavirenz, lamivudina e tenofovir disoproxil fumarato. Em pacientes com risco de disfunção renal, calcular a depuração estimada de creatinina, fósforo sérico, glicose de urina e proteína de urina antes de iniciar o tratamento com tenofovir e periodicamente durante o tratamento. Evite tomar comprimidos de efavirenz, lamivudina e tenofovir disoproxil fumarato ao mesmo tempo ou recente de drogas nefrotóxicas. (5.6)
- Sintomas Psiquiátricos Sérios: uma avaliação médica imediata é recomendada para sintomas psiquiátricos sérios, como depressão grave ou ideação suicida. (5.7, 17)
- Sintomas do Sistema Nervoso (NSS): NSS são frequentes, geralmente começam entre 1 a 2 dias após iniciar a terapia e melhora em 2 a 4 semanas. A dosagem na hora de dormir pode melhorar a tolerabilidade. NSS não são preditivos de início de sintomas psiquiátricos. (5.8, 17)
- Toxicidade Embrio-Fetal: evite a ingestão no primeiro trimestre da gravidez, pois podem ocorrer danos ao feto. (5.9, 8.1)
- Hepatotoxicidade: monitorar os testes de função hepática antes e durante o tratamento em pacientes com doença hepática subjacente, incluindo coinfecção por hepatite B ou C, elevações marcadas de transaminases ou que estão tomando medicamentos associados à toxicidade hepática. Entre os casos relatados de insuficiência hepática, alguns ocorreram em pacientes sem doença hepática préexistente. (5.11, 8.7)
- Erupção Cutânea: a erupção cutânea geralmente começa entre 1 a 2 semanas após iniciar a terapia e resolve-se dentro de 4 semanas. Interrompa se desenvolver erupções cutâneas graves. (5.10, 17)
- Convulsões: tenha cuidado em pacientes com histórico de convulsões. (5.12)
- Lípidos: elevações totais de colesterol e triglicerídeos. Monitorize antes da terapia e periodicamente depois dela. (5.13)
- Diminuição da Densidade Mineral Óssea (DMO): observado em pacientes infectados pelo HIV. Considere a avaliação da DMO em pacientes com histórico de fratura patológica ou outros fatores de risco para osteoporose ou perda óssea. (5.14)
- Síndrome de Reconstituição Imune: observado em pacientes infectados pelo HIV. Pode exigir uma avaliação e tratamento adicional. (5.15)
- Redistribuição/Acumulação de Gordura Corporal: observada em pacientes infectados com HIV que recebem terapia de combinação antiretroviral. (5.16)

REAÇÕES ADVERSAS

- As reações adversas mais comuns são: concentração prejudicada, sonhos anormais, dor de cabeça, náuseas, mal-estar, fadiga, sinais e sintomas nasais, diarréia, erupção cutânea, tonturas, insônia, dor, depressão, astenia e tosse. (6)

INTERAÇÕES MEDICAMENTOSAS

A coadministração de comprimidos de efavirenz, lamivudina e tenofovir disoproxil fumarato pode alterar as concentrações de outras drogas e outras drogas podem alterar a concentração de efavirenz, lamivudina e fumarato de tenofovir disoproxil. O potencial para interações medicamentosas deve ser considerado antes e durante a terapia. (7)

USO EM POPULAÇÕES ESPECÍFICAS

- Gravidez: as mulheres devem evitar gravidez durante o tratamento com efavirenz, os componente dos comprimidos de fumarato de efavirenz, lamivudina e tenofovir disoproxil, e durante 12 semanas após a interrupção. (5.9)
- Aleitamento: amamentação não é recomendada. (8.2)
- Potencial Reprodutivo de Homens e Mulheres: testes de gravidez e contracepção são recomendados. (8.3)
- Insuficiência Hepática: o efavirenz não é recomendado a pacientes com insuficiência hepática moderada ou grave. Tenha cuidado com pacientes que tenham insuficiência hepática leve. (8.7)
- Pacientes Pediátricos: a incidência de erupção cutânea foi maior que em adultos. (5.10, 6.1, 8.4)

Consulte 17 para INFORMAÇÕES DE COUNSELAÇÃO DO PACIENTE e rotulagem do paciente aprovada pela FDA.

Revisado: 06/2017

INFORMAÇÕES COMPLETAS DE PRESCRIÇÃO: CONTEÚDO*

ATENÇÃO: ACIDOSE LÁCTICA/HEPATOMEGALIA GRAVE COM ESTEATOSE e EXACERAÇÕES AGUDAS DA HEPATITE B PÓS-TRATAMENTO

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*As seções ou subseções omitidas das informações de prescrição completas não estão listadas.

INFORMAÇÃO COMPLETA

ATENÇÃO: ACIDOSE LÁCTICA/HEPATOMEGALIA GRAVE COM ESTEATOSE e EXACERAÇÕES AGUDAS DA HEPATITE B PÓS-TRATAMENTO

Acidose lática e hepatomegalia com esteatose, incluindo casos fatais, foram relatadas com o uso de análogos de nucleósidos, incluindo lamivudina e fumarato de tenofovir disoproxil. Suspender o tratamento se achados clínicos ou laboratoriais sugestivos de acidose lática ou hepatotoxicidade pronunciada *[ver Advertências e Precauções (5.1)]*.

Exacerbações agudas graves da hepatite B foram relatadas em pacientes coinfectados com vírus da hepatite B (VHB) e vírus da imunodeficiência humana (HIV-1) e descontinuaram a lamivudina e o fumarato de tenofovir disoproxil. Monitore a função hepática de perto nesses pacientes e, se apropriado, inicie o tratamento antihepatite B *[ver Advertências e Precauções (5.2)]*.

1 INDICAÇÕES E USO

Os comprimidos de efavirenz, lamivudina e tenofovir disoproxil e fumarato são indicados para uso isolado como um regime completo para o tratamento da infecção pelo vírus da imunodeficiência humana (HIV-1) em adultos e em pacientes pediátricos que pesam pelo menos 40 kg.

2 DOSAGEM E ADMINISTRAÇÃO

2.1 Dosagem recomendada para pacientes adultos e pediátricos pesando pelo menos 40 kg

A dose recomendada de comprimidos de efavirenz, lamivudina e tenofovir disoproxil fumarato é de 600 mg/300 mg/300 mg por via oral, uma vez ao dia. Recomenda-se que os comprimidos de efavirenz, lamivudina e tenofovir disoproxil fumarato sejam tomados em jejum, de preferência na hora de dormir. A dose na hora de dormir pode melhorar a tolerabilidade dos sintomas do sistema nervoso *[ver Advertências e Precauções (5.7), Reações Adversas (6.1) e Informação de Aconselhamento ao Paciente (17)]*. Os comprimidos de efavirenz, lamivudina e tenofovir disoproxil fumarato devem ser engolidos intactos com líquido.

2.2 Ajuste da Dose para Insuficiência Renal

Como o efavirenz, lamivudina e tenofovir disoproxil fumarato é um comprimido de combinação de dose fixa, não é recomendado para pacientes com insuficiência renal (depuração da creatinina inferior a 50 mL/min) ou pacientes com insuficiência renal em estágio terminal (ESRD) que requerem hemodiálise.

3 FORMAS DE DOSAGEM

Os Comprimidos de Fumarato, Disoproxil, Efavirenz, Lamivudina e Tenofovir estão disponíveis contendo 600 mg de efavirenz, USP, 300 mg de lamivudina, USP e 300 mg de fumarato de tenofovir disoproxil equivalente a 245 mg de tenofovir disoproxil.

- Os comprimidos de 600 mg/300 mg/300 mg são comprimidos revestidos, no formato de cápsula, por película biconvexas de cor amarela, com 'I' de um lado e '127' no outro.

4 CONTRAINDICAÇÕES

4.1 Hipersensibilidade

Os comprimidos de efavirenz, lamivudina e tenofovir disoproxil fumarato são contraindicados a doentes com uma reação de hipersensibilidade prévia a qualquer dos componentes contidos na fórmula.

5 AVISOS E PRECAUÇÕES

5.1 Acidose Lática/Hepatomegalia Grave com Esteatose

Acidose lática e hepatomegalia grave com esteatose, incluindo casos fatais, foram relatados com o uso de análogos de nucleósidos e outros antiretrovirais. A maioria desses casos ocorreram em mulheres. A obesidade e a exposição por muito tempo aos nucleósidos podem ser fatores de risco. Deve-se ter cuidado ao administrar análogos de nucleósidos a qualquer paciente com fatores de risco conhecidos para doença hepática; No entanto, também foram relatados casos que não houve fatores de risco conhecidos a pacienes. O tratamento deve ser suspenso em qualquer paciente que desenvolva achados clínicos ou laboratoriais sugestivos de acidose lática ou hepatotoxicidade pronunciada (o que pode incluir hepatomegalia e esteatose, mesmo na ausência de elevação marcada de transaminases).

5.2 Pacientes Coinfectados com HIV-1 e VHB

É recomendado que todos os pacientes com HIV-1 sejam testados quanto à presença de vírus crônico da hepatite B (VHB) antes de iniciar a terapia antiretroviral. A interrupção da terapia anti-VHB, incluindo lamivudina e fumarato de tenofovir disoproxil, pode estar associada a exacerbações agudas graves da hepatite. Os doentes infectados com VHB que param de tomar os comprimidos de efavirenz, lamivudina e tenofovir disoproxil fumarato devem ser cuidadosamente monitorizados com acompanhamento clínico e laboratorial durante, pelo menos, vários meses após a interrupção do tratamento. Se apropriado, a retomada da terapia antihepatite B pode ser justificada.

Diferenças Importantes entre os Produtos que contêm Lamivudina: os comprimidos de Lamivudina contêm uma dose mais alta do mesmo ingrediente ativo (lamivudina) do que os comprimidos EPIVIR-VHB. EPIVIR-VHB foi desenvolvido para pacientes com hepatite B crônica. A formulação e a dosagem de lamivudina em EPIVIR-VHB não são adequadas para pacientes coinfectados com HIV-1 e VHB. A segurança e a eficácia da lamivudina não foram estabelecidas para o tratamento da hepatite B crônica em pacientes coinfectados com HIV-1 e VHB. Se o tratamento com EPIVIR-VHB ou produto contendo tenofovir disoproxil fumarato, como o VIREAD, for prescrito para hepatite B crônica para um paciente com infeção não reconhecida ou não tratada com HIV-1, a emergência rápida de resistência ao HIV-1 provavelmente resultará devido à dose subterapêutica e a inadequação do tratamento de monoterapia com HIV-1.

5.3 Coadministração com Outros Produtos

Os comprimidos de efavirenz, lamivudina e tenofovir disoproxil fumarato são um produto combinado de dose fixa de efavirenz, lamivudina e fumarato de tenofovir disoproxil e não devem ser coadministrados concomitantemente com outros fármacos que contenham lamovudina, tenofovir ou emtricitabina, incluindo COMBIVIR® (lamivudina/zidovudina), EPIVIR® ou EPIVIR-VHB® (lamivudina), EPZICOM® (sulfato de abacavir/lamivudina), TRIZIVIR® (sulfato de abacavir/lamivudina/zidovudina), EMTRIVA® (emtricitabina), TRUVADA® (emtricitabina/tenofovir disoproxil fumarato), VIREAD (tenofovir disoproxil fumarato), ATRIPLA® (emtricitabina/efavirenz/tenofovir disoproxil fumarato), COMPLERA® (rilpivirina/emtricitabina/tenofovir), ou STRIBILD® (elvitegravir/cobicistat/tenofovir/emtricitabina).

Os comprimidos de efavirenz, lamivudina e tenofovir disoproxil fumarato não devem ser administrados de forma associada ao HEPSERA® (adefovir dipivoxil) *[Ver Interações Medicamentosas (7.3)]*.

5.4 Uso com Regimes Baseados em Interferão e Ribavirina

Estudos *in vitro* mostraram que a ribavirina pode reduzir a fosforilação de análogos de nucleósidos de pirimidina, como a lamivudina, um componente dos comprimidos de efavirenz, lamivudina e fumarato de tenofovir disoproxil. Embora nenhuma evidência de uma interação farmacocinética ou farmacodinâmica (por exemplo, perda de supressão virológica de HIV-1/VHC) tenha sido observada quando a ribavirina foi coadministrada com a lamivudina em pacientes coinfectados com HIV-1/VHC *[Ver Farmacologia Clínica (12.3)]*, descompensações hepáticas (algumas fatais) ocorreram em pacientes coinfectados com HIV-1/VHC que receberam terapia antiretroviral combinada para HIV-1 e interferão alfa com ou sem ribavirina. Os pacientes que recebem interferão alfa com ou sem ribavirina e lamivudina devem ser cuidadosamente monitorizados quanto a toxicidades associadas ao tratamento, especialmente a descompensação hepática. A interrupção da lamivudina deve ser considerada medicamente apropriada. A redução da dose ou a descontinuação do interferão alfa, ribavirina ou ambos também devem ser consideradas se o empeoramento das toxicidades clínicas for observado, incluindo descompensação hepática (por exemplo, Child-Pugh > 6). Veja a informação completa de prescrição para interferão e ribavirina.

5.5 Pancreatite

Em pacientes pediátricos com histórico de exposição prévia de nucleósidos antirretrovirais, histórico de pancreatite ou outros fatores de risco significativos para o desenvolvimento de pancreatite, a lamivudina deve ser usada com cuidado. O tratamento com comprimidos de efavirenz, lamivudina e tenofovir disoproxil fumarato deve ser interrompido imediatamente se ocorrerem sinais clínicos, sintomas ou anormalidades laboratoriais sugestivas de pancreatite.

5.6 Novo Início ou Piora da Insuficiência Renal

Tenofovir, um componente dos comprimidos de efavirenz, lamivudina e tenofovir disoproxil fumarato é eliminado principalmente pelo rim. A deficiência renal, incluindo casos de insuficiência renal aguda e síndrome de Fanconi (lesão tubular renal com hipofosfatemia grave), foi relatada com uso de tenofovir disoproxil fumarato [Ver Reações Adversas (6.2)].

Recomenda-se que a depuração estimada da creatinina seja avaliada em todos os pacientes antes de iniciar e durante a terapia com tenofovir disoproxil fumarato. Em pacientes com risco de disfunção renal, incluindo pacientes que já tiveram eventos renais antes de receber HEPSERA® (adefovir dipivoxil), recomenda-se que a depuração estimada de creatinina, fósforo sérico, glicose de urina e proteína de urina sejam avaliados antes do início e periodicamente durante a terapia com o tenofovir disoproxil fumarato.

Os comprimidos de efavirenz, lamivudina e tenofovir disoproxil fumarato devem ser evitados com o uso recente ou concomitante de um agente nefrotóxico (por exemplo, fármacos anti-inflamatórios não esteroides com altas doses ou múltiplas (AINEs)) [Ver Interações Medicamentosas (7.3)]. Foram notificados casos de insuficiência renal aguda após o início de doses elevadas ou múltiplos AINEs em pacientes infectados pelo HIV com fatores de risco para disfunção renal que pareciam estáveis em tenofovir disoproxil fumarato. Alguns pacientes necessitaram de hospitalização e terapia de reposição renal. Alternativas aos AINEs devem ser consideradas, se necessário, em pacientes com risco de disfunção renal.

A dor óssea persistente ou que se agrava, dor nas extremidades, fraturas e/ou dor ou fraqueza muscular podem ser manifestações da tubulopatia renal proximal e devem induzir a avaliação da função renal em pacientes em risco.

5.7 Sintomas Psiquiátricos

Experiências adversas psiquiátricas graves foram relatadas em pacientes tratados com efavirenz, um componente de efavirenz, lamivudina e comprimidos de tenofovir disoproxil fumarato. Em experiências controladas de 1008 doentes tratados com regimes contendo efavirenz para uma média de 2,1 anos e 635 doentes tratados com regimes de controle durante uma média de 1,5 anos, a frequência (independentemente da causalidade) de eventos psiquiátricos graves específicos entre os doentes que receberam efavirenz ou regimes de controle, respectivamente, foram depressão grave (2,4%, 0,9%), ideação suicida (0,7%, 0,3%), tentativas de suicídio não fatal (0,5%, 0), comportamento agressivo (0,4%, 0,5%), reações paranoicas (0,4% , 0,3%) e reações maníacas (0,2%, 0,3%). Quando os sintomas psiquiátricos parecidos aos descrito acima foram combinados e avaliados como um grupo em uma análise multifatorial dos dados do Estudo 006, o tratamento com efavirenz foi associado a uma elevação na ocorrência desses sintomas psiquiátricos selecionados. Outros fatores associados ao aumento da ocorrência desses sintomas psiquiátricos foram histórico de uso de drogas injetáveis, histórico psiquiátrico e recebimento de medicação psiquiátrica na entrada do estudo; associações semelhantes foram observadas em ambos os grupos de tratamento com efavirenz e controle. No estudo 006, o aparecimento de novos sintomas psiquiátricos sérios ocorreram ao longo do estudo para ambos os pacientes tratados com efavirenz e com controle. Um por cento dos pacientes tratados com efavirenz interromperam ou descontinuaram o tratamento por causa de um ou mais desses sintomas psiquiátricos selecionados.

Também existiram relatos ocasionais de pós-comercialização de morte por suicídio, delírios, comportamentos semelhantes a psicose e catatonia, embora uma relação causal com o uso de efavirenz não possa ser determinada a partir desses relatórios. Pacientes com experiências adversas psiquiátricas graves devem procurar uma avaliação médica imediatamente para averiguar a possibilidade de que os sintomas possam estar interligados ao uso de efavirenz e, se positivo, determinar se os riscos de terapia contínua superam os benefícios.

5.8 Sintomas do Sistema Nervoso

Cinquenta e três por cento (531/1008) dos pacientes que receberam efavirenz, um componente dos comprimidos de efavirenz, lamivudina e fumarato de tenofovir disoproxil, em ensaios controlados contaram sintomas do sistema nervoso central (qualquer grau, independentemente da causalidade) em comparação com 25% (156/635) dos pacientes que receberam regimes de controle. Estes sintomas englobavam, mas não se restrigiam a, tonturas (28,1% dos 1008 pacientes), insônia (16,3%), comprometimento da concentração (8,3%), sonolência (7,0%), sonhos anormais (6,2%) e alucinações (1,2 %). Estes sintomas foram graves em 2,0% dos pacientes e 2,1% dos pacientes suspenderam a terapia como resultado. Esses sintomas, geralmente, iniciam durante o primeiro ou segundo dia de terapia e, geralmente, se resolvem após 2 a 4 semanas de terapia. Após 4 semanas de terapia, a prevalência de sintomas do sistema nervoso de pelo menos severidade moderada variou de 5% a 9% em pacientes tratados com regimes contendo efavirenz e de 3% a 5% em pacientes tratados com um regime de controle. Os pacientes devem ser informados de que esses sintomas comuns provavelmente melhorarão com a terapia contínua e não foram preditivos do início subsequente dos sintomas psiquiátricos menos frequentes *[Ver Avisos e Precauções (5.7)]*. A dose na hora de dormir pode melhorar a tolerabilidade desses sintomas do sistema nervoso *[Ver Dosagem e Administração (2.1)]*.

A análise dos dados de longo prazo do Estudo 006 (seguimento médio de 180 semanas, 102 semanas e 76 semanas para pacientes tratados com efavirenz + zidovudina + lamivudina, efavirenz + indinavir e indinavir + zidovudina + lamivudina, respectivamente) mostraram que, além de 24 semanas de terapia, a incidência de sintomas do sistema nervoso de novo aparecimento entre os pacientes tratados com efavirenz era geralmente semelhante à do braço de controle contendo indinavir.

Os pacientes que recebem efavirenz devem ser alertados sobre o potencial de efeitos aditivos do sistema nervoso central quando o efavirenz for utilizado concomitantemente com álcool ou drogas psicoativas. Os pacientes que apresentem sintomas do sistema nervoso central, como tonturas, distúrbios de concentração e/ou sonolência, devem evitar tarefas potencialmente perigosas, como dirigir ou operar máquinas.

5.9 Toxicidade Embionária

Efavirenz, um componente dos comprimidos de efavirenz, lamivudina e tenofovir disoproxil fumarato, pode causar dano fetal quando ingerido durante o primeiro trimestre de gravidez por mulheres grávidas. Aconselhe as mulheresdo que estão administrando o efavirenz para evitar a gravidez. *[Ver Uso em Populações Específicas (8.1).]*

5.10 Erupção Cutânea

Em ensaios clínicos controlados, 26% (266/1008) de pacientes tratados com 600 mg de efavirenz apresentaram erupção cutânea, em comparação com 17% (111/635) de pacientes tratados em grupos de controle. A erupção associada a bolhas, desquamação úmida ou ulceração ocorreram em 0,9% (9/1008) dos pacientes tratados com efavirenz. A incidência de erupção cutânea de grau 4 (por exemplo, eritema multiforme, síndrome de Stevens-Johnson) em pacientes tratados com efavirenz em todos os estudos e acesso expandido foi de 0,1%. As erupções cutâneas são geralmente erupções maculopapulares moderadas a moderadas que ocorrem nas primeiras 2 semanas após o início da terapia com efavirenz (o tempo médio de início da erupção cutânea em adultos foi de 11 dias) e, na maioria dos pacientes com terapia contínua com efavirenz, a erupção cutânea melhora dentro de 1 mês (duração média, 16 dias). A taxa de descontinuação da erupção cutânea em ensaios clínicos foi de 1,7% (17/1008).

O efavirenz geralmente pode ser reiniciado em pacientes que interrompem a terapia devido à erupção cutânea. O efavirenz deve ser parado em doentes que venham a desenvolver erupção cutânea grave associada a bolhas, desquamação, envolvimento da mucosa ou febre. Anti-histamínicos e/ou corticosteroides adequados podem melhorar a tolerabilidade e acelerar a resolução da erupção cutânea. Para pacientes que tiveram uma reação cutânea com risco de vida (por exemplo, síndrome de Stephens-Johnson), a terapia alternativa deve ser considerada *[Ver Contraindicações (4.1)]*.

A erupção cutânea foi relatada em 26 dos 57 pacientes pediátricos (46%) tratados com cápsulas de efavirenz. Um paciente pediátrico apresentou erupção cutânea de grau 3 (erupções cutâneas confluentes com febre) e dois pacientes apresentaram erupção cutânea de grau 4 (eritema multiforme). O tempo médio de início da erupção cutânea em pacientes pediátricos foi de 8 dias. Deve ser considerada a profilaxia com anti-histamínicos apropriados antes do início da terapêutica com efavirenz em doentes pediátricos.

5.11 Hepatotoxicidade

O controle de enzimas hepáticas antes e durante o tratamento é indicado para pacientes com doença hepática subjacente, incluindo infecção por hepatite B ou C; pacientes com elevação marcada de transaminases; e pacientes tratados com outros medicamentos associados à toxicidade hepática *[Ver Uso em Populações Específicas (8.7)]*. Alguns dos relatórios pós-comercialização de falha hepática ocorreram em pacientes sem doença hepática pré-existente ou outros fatores de risco identificáveis *[Ver Reações Adversas (6.2)]*. O controle da enzima hepática …

… cushingóide" em pacientes que receberam terapia antiretroviral combinada. O mecanismo e as consequências a longo prazo desses eventos são desconhecidos atualmente. Não foi estabelecida uma relação causal.

5.17 Prolongamento do QTC

O prolongamento QTc foi observado com o uso de efavirenz *[Ver Interações Medicamentosas (7.2, 7.5) e Farmacologia Clínica (12.2)]*. Considere alternativas ao efavirenz quando coadministrado com um medicamento com risco conhecido de Torsade de Pointes ou quando administrado em pacientes com maior risco de Torsade de Pointes.

6 REAÇÕES ADVERSAS

As seguintes reações adversas são discutidas em outras seções da rotulagem:

- Acidose Lática/Hepatomegalia Grave com Esteatose *[Ver Advertência, Avisos e Precauções na Caixa (5.1)]*.
- Exacerbações da Hepatite B *[Ver Advertência, Avisos e Precauções na Caixa (5.2)]*.
- Descompensação Hepática em Pacientes Coinfectados com HIV-1 e Hepatite C *[Ver Advertências e Precauções (5.4)]*.
- Pancreatite *[Ver Advertências e Precauções (5.5)]*.
- Nova Aparência ou Piora da Insuficiência Renal *[Ver Avisos e Precauções (5.6)]*.
- Sintomas Psiquiátricos *[Ver Avisos e Precauções (5.7)]*.
- Sintomas do Sistema Nervoso *[Ver Avisos e Precauções (5.8)]*.
- Erupção Cutânea *[Ver Avisos e Precauções (5.10)]*.
- Diminuição da Densidade Mineral Óssea *[Ver Advertências e Precauções (5.14)]*.
- Síndrome de Reconstituição Imune *[Ver Avisos e Precauções (5.15)]*.
- Redistribuição de Gordura *[Ver Avisos e Precauções (5.16)]*.

6.1 Experiência de Ensaios Clínicos

Como os estudos clínicos são acompanhados em condições amplamente variáveis, as taxas de reações adversas relatadas não podem ser diretamente comparadas às taxas de outros estudos clínicos e podem não refletir as taxas observadas na prática clínica.

Efavirenz, Lamivudina e Tenofovir Disoproxil Fumarate

Pacientes com Tratamento-Naïve

Estudo 903 - Reações Adversas ao Tratamento: as reações adversas mais comuns observadas em um estudo comparativo em que 600 pessoas de um tratamento receberam tenofovir disoproxil fumarato (N = 299) ou estavudina (N = 301) em associação com lamivudina e efavirenz por 144 semanas (estudo 903) foram eventos gastrointestinais leves a moderados e tonturas.

A ocorrência de reações adversas leves (Grau 1) foi comum, com incidência semelhante em ambos os grupos, e incluiu tonturas, diarreia e náuseas. A Tabela 1 mostra um resumo de uma seleção de reações adversas, de moderadas a graves, emergentes do tratamento.

Tabela 1. Seleção de Reações Adversas Emergentes do Tratamento[a] (Graus 2 a 4) Relatadas em ≥ 5% em Qualquer Grupo de Tratamento no Estudo 903 (0 a 144 Semanas)

	Fumarato de Tenofovir Disoproxil + 3TC + EFV	d4T + 3TC + EFV
	N=299	N=301
Corpo no Geral		
Dor de cabeça	14%	17%
Dor	13%	12%
Febre	8%	7%
Dor abdominal	7%	12%
Dor lombar	9%	8%
Astenia	6%	7%
Sistema digestivo		
Diarreia	11%	13%
Náusea	8%	9%
Dispepsia	4%	5%
Vómitos	5%	9%
Perturbações do Metabolismo		
Lipodistrofia[b]	1%	8%
Sistema Musculoesquelético		
Artralgia	5%	7%
Mialgia	3%	5%
Sistema Nervoso		
Depressão	11%	10%
Insónias	5%	8%
Tonturas	3%	6%
Neuropatia periférica[c]	1%	5%
Ansiedade	6%	6%
Sistema Respiratório		
Pneumonia	5%	5%
Pele e Apêndices		
Evento de erupção cutânea[d]	18%	12%

a As frequências das reações adversas são baseadas em todos os eventos adversos emergentes do tratamento, independentemente do relacionamento com o medicamento em estudo.
b A lipodistrofia representa uma variedade de eventos adversos descritos pelo investigador e não uma síndrome definida pelo protocolo.
c A neuropatia periférica inclui neurite periférica e neuropatia.
d O evento de erupção cutânea inclui erupção cutânea, prurido, erupção cutânea maculopapular, urticária, erupção cutânea vesicobolhosa e erupção cutânea pustulosa.

Anomalias Laboratoriais: Com excepção do aumento em jejum do colesterol e dos triglicéridos, que foi mais comum no grupo da estavudina (40% e 9%) em comparação com o grupo do fumarato de tenofovir disoproxil (19% e 1%), respetivamente, as anomalias laboratoriais observadas neste estudo ocorreram com frequência semelhante nos grupos de tratamento com fumarato de tenofovir disoproxil e estavudina. A Tabela 2 mostra um resumo das anomalias laboratoriais de Graus 3 e 4.

Tabela 2. Anomalias Laboratoriais de Grau 3/4 Relatadas em ≥1% de Doentes Aleatorizados com Efavirenz, Lamivudina e Fumarato de Tenofovir Disoproxil no Estudo 903 (0 a 144 Semanas)

	Fumarato de Tenofovir Disoproxil + 3TC + EFV	d4T + 3TC + EFV
	N=299	N=301
Qualquer ≥ Anomalia Laboratorial de Grau 3	36%	42%
Colesterol em jejum (> 240 mg/dL)	19%	40%
Creatina Quinase (M: > 990 U/L; F: > 845 U/L)	12%	12%
Amilase Sérica (> 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%
Hematúria (>100 HM/CGA)	7%	7%
Neutrófilos (< 750/mm³)	3%	1%
Colesterol em jejum (> 750 mg/dL)	1%	9%

Alterações na Densidade Mineral Óssea: Em indivíduos adultos infetados com VIH-1 no Estudo 903, houve uma diminuição percentual média significativamente maior, em relação à avaliação inicial, da DMO na coluna lombar em indivíduos que receberam fumarato de tenofovir disoproxil + lamivudina + efavirenz (-2,2% ± 3,9) em comparação com indivíduos que receberam estavudina + lamivudina + efavirenz (-1,0% ± 4,6) durante 144 semanas. As alterações da DMO na anca foram semelhantes entre os dois grupos de tratamento (-2,8% ± 3,5 no grupo do fumarato de tenofovir disoproxil vs. -2,4% ± 4,5 no grupo da estavudina). Em ambos os grupos, a maioria da redução da DMO ocorreu nas primeiras 24-48 semanas do ensaio e essa redução foi mantida na Semana 144. Vinte e oito por cento dos indivíduos tratados com fumarato de tenofovir disoproxil vs. 21% dos indivíduos tratados com estavudina perderam pelo menos 5% da DMO na coluna vertebral ou 7% da DMO na anca. Fraturas clinicamente relevantes (excluindo dedos das mãos e dedos dos pés) foram relatadas em 4 indivíduos no grupo do fumarato de tenofovir disoproxil e em 6 indivíduos no grupo da estavudina. Além disso, houve aumento significativo nos marcadores bioquímicos do metabolismo ósseo (fosfatase alcalina ósseo-específica no soro, osteocalcina sérica, C-telopéptido sérico e N-telopéptido urinário) e concentrações séricas aumentadas da hormona paratiróide e da 1,25-vitamina D no grupo do fumarato de tenofovir disoproxil em relação ao grupo da estavudina. No entanto, com exceção da fosfatase alcalina ósseo-específica, essas alterações resultaram em valores que permaneceram dentro do intervalo normal *[ver Advertências e Precauções (5.14)]*.

Pediatria

Efavirenz: As reações adversas observadas em ≥10% dos 57 doentes pediátricos com idades entre 3 e 16 anos que receberam cápsulas de efavirenz, nelfinavir e um ou mais NITR no Estudo ACTG 382 incluíram erupção cutânea (46%), diarreia/fezes soltas (39%), febre (21%), tosse (16%), tonturas/vertigens/desmaios (16%), dor/sofrimento/desconforto (14%), náuseas/vómitos (12%), e dor de cabeça (11%). A incidência de sintomas do sistema nervoso foi de 18% (10/57). Um doente experimentou erupção cutânea de Grau 3, dois doentes apresentaram erupção cutânea de Grau 4 e cinco doentes (9%) interromperam o tratamento devido a erupção cutânea *[ver Advertências e Precauções (5.10)]*.

Fumarato de Tenofovir Disoproxil: A avaliação das reações adversas baseia-se em dois ensaios clínicos aleatorizados (Estudos 352 e 321) em 184 doentes pediátricos infetados com VIH-1 (2 até menos de 18 anos de idade) que receberam tratamento com fumarato de tenofovir disoproxil (N = 93) ou placebo/comparador ativo (N = 91) em combinação com outros agentes anti-retrovirais durante 48 semanas. As reações adversas observadas em indivíduos que receberam tratamento com fumarato de tenofovir disoproxil foram consistentes com as observadas em ensaios clínicos com adultos.

Alterações na Densidade Mineral Óssea: Ensaios clínicos em crianças e adolescentes infetados com VIH-1 avaliaram as alterações da DMO. No Estudo 321 (12 até menos de 18 anos), a taxa média de ganho de DMO na Semana 48 foi menor no grupo do fumarato de tenofovir disoproxil em comparação com o grupo de tratamento com placebo. Seis indivíduos tratados com fumarato de tenofovir disoproxil e um indivíduo tratado com placebo apresentaram perda significativa (maior que 4%) de DMO na coluna lombar na Semana 48. As alterações dos índices Z da avaliação inicial da DMO foram de -0,341 para a coluna lombar e -0,458 para a totalidade do corpo nos 28 indivíduos que foram tratados com fumarato de tenofovir disoproxil durante 96 semanas. No Estudo 352 (2 até menos de 12 anos), a taxa média de ganho de DMO na Semana 48 foi semelhante entre o grupo do fumarato de tenofovir disoproxil e os grupos de tratamento com d4T ou AZT. O ganho de DMO na totalidade do corpo foi menor no grupo do fumarato de tenofovir disoproxil em comparação com os grupos de tratamento com d4T ou AZT. Um indivíduo tratado com fumarato de tenofovir disoproxil e nenhum dos indivíduos tratados com d4T ou AZT experimentou perda significativa de DMO da coluna lombar (maior que 4%) na Semana 48. As alterações dos índices Z da avaliação inicial da DMO foram de -0,012 para a coluna lombar e -0,338 para a totalidade do corpo nos 64 indivíduos que foram tratados com fumarato de tenofovir disoproxil durante 96 semanas. Em ambos os ensaios, o crescimento do esqueleto (altura) pareceu não ser afetado *[ver Advertências e Precauções (5.14)]*.

6.2 Experiência Pós-comercialização

As seguintes reações adversas foram identificadas durante o uso pós-aprovação para cada um dos componentes individuais de efavirenz, lamivudina, e comprimidos de fumarato de tenofovir disoproxil. Como estas reações são relatadas voluntariamente a partir de uma população de tamanho desconhecido, nem sempre é possível estimar de forma confiável a sua frequência ou estabelecer relações causais com a exposição ao medicamento. Estas reações foram escolhidas para inclusão devido a uma combinação da sua gravidade, frequência dos relatos, ou potencial conexão causal com o efavirenz, lamivudina e fumarato de tenofovir disoproxil.

Efavirenz

Corpo no Geral: reações alérgicas, astenia, redistribuição/acumulação da gordura corporal *[ver Advertências e Precauções (5.16)]*.

Sistema Nervoso Central e Periférico: coordenação anormal, ataxia, coordenação cerebelar e distúrbios do equilíbrio, convulsões, hipoestesia, parestesia, neuropatia, tremores, vertigens.

Sistema Endócrino: ginecomastia.

Sistema Gastrointestinal: obstipação, má absorção.

Sistema Cardiovascular: rubor, palpitações.

Sistema Hepático e Biliar: aumento da enzima hepática, insuficiência hepática, hepatite. Alguns dos relatos pós-comercialização de insuficiência hepática, incluindo casos em doentes sem doença hepática pré-existente ou outros fatores de risco identificáveis, foram caracterizados por um curso fulminante, progredindo em alguns casos para transplante ou morte.

Sistema Metabólico e Nutricional: hipercolesterolemia, hipertrigliceridemia.

Sistema Musculoesquelético: artralgia, mialgia, miopatia.

Componente Psiquiátrica: reações agressivas, agitação, delírios, labilidade emocional, mania, neurose, paranoia, psicose, suicídio, catatonia.

Sistema Respiratório: dispneia.

Pele e Apêndices: eritema multiforme, dermatite fotoalérgica, síndrome de Stevens-Johnson.

Órgãos dos Sentidos: visão anormal, zumbido.

Lamivudina

Corpo no Geral: redistribuição/acumulação da gordura corporal *[ver Advertências e Precauções (5.16)]*.

Sistemas Endócrino e Metabólico: hiperglicemia.

Geral: fraqueza.

Sistemas Sanguíneo e Linfático: anemia (incluindo aplasia dos glóbulos vermelhos puros e anemias graves que progridem na terapia).

Sistemas Hepático e Pancreático: acidose lática e esteatose hepática, exacerbação pós-tratamento da hepatite B *[ver Advertência em Quadro Destacado, Advertências e Precauções (5.1, 5.2)]*.

Hipersensibilidade: anafilaxia, urticária.

Sistema Musculoesquelético: fraqueza muscular, elevação de CPK, rabdomiólise.

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Tabela 3. Interações Medicamentosas Demonstradas e Outras Potencialmente Significativas: A Alteração na Dose ou Regime Pode Ser Recomendada Com Base em Estudos de Interação Medicamentosa ou na Interação Prevista.

Medicamento Concomitante Classe: Nome do Medicamento	Efeito	Comentário Clínico
Anticoagulante: Varfarina	↑ ou ↓ varfarina	Monitorizar o INR e ajustar a dose de varfarina, se necessário.
Anticonvulsivantes: Carbamazepina	↓ carbamazepina* ↓ efavirenz*	Não existem dados suficientes para fazer uma recomendação de dose para efavirenz. Deve ser utilizado um tratamento anticonvulsivo alternativo.
Fenitoína Fenobarbital	↓ anticonvulsivante ↓ efavirenz	Monitorizar os níveis plasmáticos do anticonvulsivante periodicamente devido ao potencial de redução nos níveis plasmáticos do anticonvulsivante e/ou efavirenz.
Antidepressivos: Bupropiona	↓ bupropiona*	Os aumentos na dose de bupropiona devem ser orientados pela resposta clínica. A dose de bupropiona não deve exceder a dose máxima recomendada.
Sertralina	↓ sertralina*	Os aumentos na dose de sertralina devem ser orientados pela resposta clínica.
Antifúngicos: Itraconazol Cetoconazol	↓itraconazol* ↓hidroxi-itraconazol* ↓cetoconazol	Deve ser considerado um tratamento antifúngico alternativo porque nenhuma recomendação de dose para itraconazol ou cetoconazol pode ser feita.
Posaconazol	↓posaconazol*	Evitar o uso concomitante, a menos que o benefício supere os riscos.
Anti-infecioso: Claritromicina	↓claritromicina* ↑ metabolito 14-OH*	Devem ser consideradas alternativas aos antibióticos macrólidos devido ao risco de prolongamento do intervalo QT.
Anti-micobacteriano: Rifabutina	↓ rifabutina*	Aumentar a dose diária de rifabutina em 50%. Deve ser considerada a duplicação da dose de rifabutina em regimes nos quais a rifabutina é administrada 2 ou 3 vezes por semana.
Antimaláricos Arteméter/lumefantrina	↓ arteméter* ↓ dihidroartemisinina* ↓ lumefantrina*	Devem ser consideradas alternativas ao arteméter/lumefantrina devido ao risco de prolongamento do intervalo QT.
Atovaquona/proguanil	↓ atovaquona ↓ proguanil	A administração concomitante não é recomendada.
Bloqueadores dos canais de cálcio: Diltiazem	↓ diltiazem* ↓ desacetil diltiazem* ↓ N-monodesmetil diltiazem*	Os ajustes da dose de diltiazem devem ser orientados pela resposta clínica (consultar a informação de prescrição completa do diltiazem).
Outros (por exemplo, felodipina, nicardipina, nifedipina, verapamil)	↓ ibloqueador dos canais de cálcio	Quando coadministrado com efavirenz, o ajuste da dose do bloqueador dos canais de cálcio pode ser necessário e deve ser orientado pela resposta clínica (consultar a informação de prescrição completa do bloqueador dos canais de cálcio).
Inibidores da HMG-CoA redutase: Atorvastatina Pravastatina Sinvastatina	↓atorvastatina* ↓pravastatina* ↓sinvastatina*	As concentrações plasmáticas de atorvastatina, pravastatina e sinvastatina diminuíram. Consultar a informação de prescrição completa do inibidor da HMG-CoA redutase para orientação sobre a individualização da dose.
Agentes antivirais da hepatite C: Boceprevir	↓ boceprevir*	A administração concomitante de boceprevir não é recomendada.
Simeprevir	↓ simeprevir* ↔ efavirenz	A administração concomitante de simeprevir não é recomendada.
Ledipasvir/Sofosbuvir	↑ fumarato de tenofovir disoproxil	Monitorizar as reações adversas associadas com fumarato de tenofovir disoproxil.
Agentes antivirais da hepatite B: Adefovir dipivoxil		A administração concomitante de adefovir dipivoxil não é recomendada.
Contracetivos hormonais: Etinilestradiol/Norgestimato via oral	↓ metabolitos ativos de norgestimato*	Deve ser utilizado um método contracetivo de barreira confiável além de contracetivos hormonais.
Implante de etonogestrel	↓ etonogestrel	Deve ser utilizado um método contracetivo de barreira confiável além de contracetivos hormonais. A interação entre etonogestrel e efavirenz não foi estudada. Pode ser esperada uma diminuição da exposição ao etonogestrel. Ocorreram ocasionalmente notificações pós-comercialização de falha do método contracetivo com etonogestrel em doentes expostos ao efavirenz.
Imunossupressores: Ciclosporina, tacrolimus, sirolimus, e outros metabolizados pela CYP3A	↓ imunossupressor	Podem ser necessários ajustes de dose do imunossupressor. É recomendado uma monitorização rigorosa das concentrações de imunossupressores durante pelo menos 2 semanas (até serem atingidas concentrações estáveis) ao iniciar ou parar o tratamento com efavirenz.
Analgésico narcótico: Metadona	↓ metadona*	Monitorizar sinais de privação de metadona e, se necessário, aumentar a dose de metadona para aliviar os sintomas de abstinência.

* A interação entre efavirenz e o medicamento foi avaliada num estudo clínico. Estão previstas todas as outras interações medicamentosas mostradas.

Esta tabela não é abrangente.

7.6 Medicamentos sem Interações Clínicas Significativas

Não é recomendado nenhum ajuste de dosagem quando os comprimidos de efavirenz, lamivudina e fumarato de tenofovir disoproxil são administrados com o seguinte: antiácidos de hidróxido de alumínio/magnésio, azitromicina, cetirizina, famotidina, fluconazol e lorazepam.

8 USO EM POPULAÇÕES ESPECÍFICAS

8.1 Gravidez

Efavirenz:

Resumo dos Riscos: Existem relatos de casos retrospetivos de defeitos do tubo neural em lactentes cujas mães foram expostas a regimes contendo efavirenz no primeiro trimestre da gravidez. Os dados prospetivos de gravidez do Registo Antirretrovírico de Gravidez não são suficientes para avaliar adequadamente esse risco. Os dados disponíveis do Registo Antirretrovírico de Gravidez não mostram diferença no risco geral de malformações congénitas graves quando comparados com a taxa do histórico de ocorrências de malformações congénitas graves em 2,7% da população de referência dos EUA inserida no Programa de Malformações Congénitas da Área Metropolitana de Atlanta (MACDP). Embora não tenha sido estabelecida uma relação causal entre a exposição ao efavirenz no primeiro trimestre e os defeitos do tubo neural, foram observadas malformações semelhantes em estudos realizados em macacos com doses similares à dose humana. Além disso, ocorreram toxicidades fetais e embrionárias em ratos, numa dose dez vezes inferior à exposição humana na dose clínica recomendada. Devido ao risco potencial de defeitos no tubo neural, o efavirenz não deve ser utilizado no primeiro trimestre da gravidez. As mulheres grávidas devem ser avisadas do risco potencial para o feto.

Dados: Dados Humanos: Existem relatórios pós-comercialização retrospetivos de resultados consistentes com os defeitos do tubo neural, incluindo meningomielocele, tudo em recém-nascidos de mães expostas a regimes contendo efavirenz no primeiro trimestre.

Com base em relatórios prospetivos do Registo Antirretrovírico de Gravidez (APR) de cerca de 1000 nados-vivos após exposição a regimes contendo efavirenz (incluindo mais de 800 nados-vivos expostos no primeiro trimestre), não houve diferença na relação entre o efavirenz e as malformações congénitas gerais quando comparado com a taxa do histórico de ocorrência de malformações congénitas em 2,7% da população de referência dos EUA inserida no Programa de Malformações Congénitas da Área Metropolitana de Atlanta (MACDP). A partir do relatório intercalar do APR emitido em dezembro de 2014, a prevalência de malformações congénitas após exposição no primeiro trimestre foi de 2,3% (95% IC: 1,4% -3,6%). Um desses defeitos prospectivamente relatados com exposição de primeiro trimestre foi um defeito no tubo neural. Um único caso de anoftalmia com exposição no primeiro trimestre ao efavirenz também foi relatado prospectivamente. Esse caso incluiu também fendas faciais oblíquas severas e bandas amnióticas, que têm uma associação conhecida com anoftalmia.

Dados Animais: Os efeitos do efavirenz no desenvolvimento embrio-fetal foram estudados em três espécies não-clínicas (macacos cinomolgos, ratos e coelhos). Nos macacos, foi administrado efavirenz 60 mg/kg/dia a fêmeas grávidas durante toda a gravidez (dias 20 a 150 de gestação). As exposições sistémicas maternas ao medicamento (ASC) foram 1,3 vezes a exposição em humanos na dose clínica recomendada (600 mg/dia), com concentrações de medicamento na veia umbilical dos fetos aproximadamente igual a 0,7 vezes os valores maternos. Três de 20 fetos/recém-nascidos tiveram uma ou mais malformações. Não houve fetos ou recém-nascidos malformados de mães tratadas com placebo. As malformações que ocorreram nesses três fetos de macaco incluíam anencefalia e anoftalmia unilateral num feto, microftalmia num outro feto e fenda do palato num terceiro feto. Não se estabeleceu um NSEAO (nível sem efeitos adversos observáveis) para este estudo porque apenas uma dosagem foi avaliada. Nos ratos, o efavirenz foi administrado durante o período da organogénese (dias 7 a 18 de gestação) ou a partir do dia 7 de gestação até ao dia 21 de aleitamento, 50, 100 ou 200 mg/ kg/dia. A administração de 200 mg/kg/dia em ratos foi associada ao aumento da incidência de reabsorções precoces, e doses de 100 mg/kg/dia ou maiores foram associadas à mortalidade neonatal precoce. A ASC no NSEAO (50 mg/kg/dia) neste estudo de ratos foi 0,1 vezes a dos humanos na dose clínica recomendada. As concentrações de medicamento no leite ao dia 10 de aleitamento foram aproximadamente 8 vezes maiores do que as do plasma materno. Em coelhas grávidas, o efavirenz não foi letal para o embrião nem teratogénico quando administrado em doses de 25, 50 e 75 mg/kg/dia durante o período de organogénese (dias 6 a 18 de gestação). A ASC no NSEAO (75 mg/kg/dia) em coelhos foi 0,4 vezes a dos humanos na dose clínica recomendada.

Lamivudina:

Resumo dos Riscos: Os dados disponíveis do Registo Antirretrovírico de Gravidez não mostram diferença no risco geral de malformações congénitas graves para a lamivudina quando comparados com a taxa do histórico de ocorrência de malformações congénitas graves em 2,7% da população de referência dos EUA inserida no Programa de Malformações Congénitas da Área Metropolitana de Atlanta (MACDP). A lamivudina produziu toxicidade embrionária em coelhos numa dose que produziu exposições humanas semelhantes à dose clínica recomendada. A relevância das descobertas em estudos com animais para os dados de registo da gravidez humana não é conhecida.

Dados: Dados Humanos: Com base em relatórios prospetivos do Registo Antirretrovírico de Gravidez de mais de 11.000 exposições à lamivudina durante uma gravidez resultante em nados-vivos (incluindo mais de 4.300 nados-vivos que foram expostos no primeiro trimestre), não houve diferença na relação entre a lamivudina e as malformações congénitas gerais quando comparado com a taxa de ocorrência de malformações congénitas em 2,7% da população de referência dos EUA inserida no MACDP. A prevalência de defeitos no primeiro trimestre foi de 3,1% (95% IC: 2,6% a 3,7%).

A farmacocinética da lamivudina foi estudada em mulheres grávidas durante 2 ensaios clínicos realizados na África do Sul. Os ensaios avaliaram a farmacocinética em 16 mulheres com 36 semanas de gravidez usando 150 mg de lamivudina duas vezes ao dia com zidovudina, 10 mulheres com 38 semanas de gravidez usando 150 mg de lamivudina duas vezes ao dia com zidovudina, e 10 mulheres com 38 semanas de gravidez com lamivudina 300 mg duas vezes ao dia sem outros antirretrovirais. Esses ensaios não foram projetados ou alimentados de forma a fornecerem informações de eficácia.

A farmacocinética da lamivudina em mulheres grávidas foi semelhante à observada em adultas não grávidas e em mulheres pós-parto. As concentrações de lamivudina foram geralmente similares nas amostras de soro materno, neonatal e do cordão umbilical. Num subconjunto de indivíduos, as amostras de líquido amniótico foram recolhidas após a rutura natural das membranas e confirmaram que a lamivudina atravessa a placenta em humanos. As concentrações de lamivudina no líquido amniótico foram tipicamente 2 vezes maiores do que os níveis séricos maternos e variaram entre 1,2 e 2,5 mcg por ml (150 mg duas vezes ao dia), e entre 2,1 e 5,2 mcg por ml (300 mg duas vezes ao dia).

Dados Animais: Estudos com ratas grávidas mostraram que a lamivudina é transferida para o feto através da placenta. Foram realizados estudos de reprodução com lamivudina administrada por via oral em ratos e coelhos com doses que produzem níveis plasmáticos até aproximadamente 35 vezes a da dose recomendada para terapia anti-VIH de adultos. Não foi observada evidência de teratogenicidade devido à lamivudina. Foi observada a evidência de letalidade embrionária no coelho em níveis de exposição semelhantes aos observados em seres humanos, mas não houve indicação desse efeito no rato em níveis de exposição até 35 vezes a dos humanos.

Fumarato de Tenofovir Disoproxil:

Não há estudos adequados e bem controlados em mulheres grávidas. Como os estudos de reprodução em animais nem sempre predizem a resposta humana, o fumarato de tenofovir disoproxil deve ser usado durante a gravidez apenas se for manifestamente necessário.

Dados Animais: Foram realizados estudos de reprodução em ratos e coelhos com doses até 14 e 19 vezes a dose humana com base na comparação das áreas de superfície corporal, e não revelaram evidências de comprometimento da fertilidade ou danos ao feto devido ao tenofovir.

8.2 Aleitamento

Os Centros de Controlo e Prevenção de Doenças (CDC) recomendam que as mães infetadas com VIH-1 não amamentem os seus bebés para evitar o risco de transmissão pós-natal da infeção pelo VIH-1. Devido ao potencial de transmissão de VIH-1 a bebés amamentados, as mulheres devem ser aconselhadas a não amamentar.

Efavirenz: Foi demonstrado que o efavirenz passa para o leite materno humano.

Lamivudina: A lamivudina é excretada no leite humano. As amostras de leite materno obtidas de 20 mães que receberam monoterapia de lamivudina (300 mg duas vezes por dia) ou terapia de combinação (150 mg de lamivudina duas vezes ao dia e 300 mg de zidovudina duas vezes ao dia) tinham concentrações mensuráveis de lamivudina.

Fumarato de Tenofovir Disoproxil: As amostras de leite materno obtidas de cinco mães infetadas pelo VIH-1 na primeira semana pós-parto mostram que o tenofovir é excretado no leite humano em níveis baixos. O impacto desta exposição em lactentes amamentados é desconhecido.

8.3 Mulheres e Homens com Potencial Reprodutivo

Devido a potenciais efeitos teratogénicos, a gravidez deve ser evitada em mulheres que recebam comprimidos de efavirenz, lamivudina e fumarato de tenofovir disoproxil. *[Ver Uso em Populações Específicas (8.1).]*

Testes de Gravidez: As mulheres com potencial reprodutivo devem ser submetidas a testes de gravidez antes do início dos comprimidos de efavirenz, lamivudina e fumarato de tenofovir disoproxil.

Contraceção: As mulheres com potencial reprodutivo devem usar contraceção eficaz durante o tratamento com comprimidos de efavirenz, lamivudina e fumarato de tenofovir disoproxil, e durante 12 semanas após a interrupção dos comprimidos de efavirenz, lamivudina e fumarato de tenofovir disoproxil devido à longa vida útil do efavirenz. A contraceção de barreira deve ser sempre utilizada em associação com outros métodos de contraceção. Os métodos hormonais que contêm progesterona podem ter uma eficácia diminuída *[ver Interações Medicamentosas (7.5)]*.

8.4 Uso Pediátrico

Os comprimidos de efavirenz, lamivudina e fumarato de tenofovir disoproxil só devem ser administrados a doentes com um peso corporal superior ou igual a 40 kg.

8.5 Uso Geriátrico

Os estudos clínicos de efavirenz, lamivudina e fumarato de tenofovir disoproxil não incluíram um número suficiente de indivíduos com idade igual ou superior a 65 anos para determinar se eles respondem de forma diferente dos indivíduos mais jovens. Em geral, devem ser tomadas precauções na administração de lamivudina em doentes idosos, refletindo a maior frequência de diminuição da função hepática, renal ou cardíaca, e de doença concomitante ou outra terapia medicamentosa.

8.6 Doentes com Compromisso Renal

Os comprimidos de efavirenz, lamivudina e fumarato de tenofovir disoproxil não são recomendados para doentes com compromisso renal (ou seja, depuração da creatinina inferior a 50 ml/min) ou com doença renal em fase terminal (ESRD) que requer hemodiálise, porque fazem parte de uma formulação com combinação em dose fixa que não pode ser ajustada.

8.7 Insuficiência Hepática

Os comprimidos de efavirenz, um componente de efavirenz, lamivudina e fumarato de tenofovir disoproxil não são recomendados para doentes com insuficiência hepática moderada ou grave porque não há dados suficientes para determinar se é necessário o ajuste da dose. Os doentes com insuficiência hepática ligeira podem ser tratados com efavirenz sem qualquer ajuste da dose. Devido ao extenso metabolismo mediado pelo citocromo P450 do efavirenz e à experiência clínica limitada em doentes com insuficiência hepática, devem ser tomadas precauções na administração de efavirenz a estes doentes *[ver Advertências e Precauções (5.11) e Farmacologia Clínica (12.3)]*.

10 SOBREDOSAGEM

Se ocorrer sobredosagem, o doente tem de ser monitorizado para pesquisa de toxicidade e, conforme necessário, deve ser administrado tratamento padrão de apoio.

Efavirenz: Alguns doentes que tomaram acidentalmente 600 mg duas vezes por dia relataram um aumento de sintomas do sistema nervoso. Um doente apresentou contrações musculares involuntárias.

O tratamento da sobredosagem com efavirenz deve consistir em medidas gerais de apoio, incluindo a monitorização dos sinais vitais e observação do estado clínico do doente. A administração de carvão ativado pode ser usada para auxiliar a remoção de medicamento não absorvido. Não existe um antídoto específico para a sobredosagem com efavirenz. Uma vez que o efavirenz é altamente ligado a proteínas, é improvável que a diálise remova significativamente o medicamento do sangue.

Lamivudina: Não existe um tratamento específico para a sobredosagem com lamivudina. Se ocorrer sobredosagem, o doente tem de ser monitorizado e, conforme necessário, deve ser administrado tratamento padrão de apoio porque uma quantidade negligenciável de lamivudina foi removida via (4 horas) de hemodiálise, diálise peritoneal contínua ambulatória e diálise peritoneal automática, e não se sabe se a hemodiálise contínua proporcionaria benefício clínico num evento de sobredosagem de lamivudina.

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Lamivudina: Após administração oral de 2 mg/kg de lamivudina duas vezes ao dia em 9 adultos com VIH-1, o pico da concentração ($C_{máx}$) sérica de lamivudina foi 1,5 ± 0,5 mcg/ml (média ± DP). A área sob a curva de concentração plasmática versus tempo (ASC) e a $C_{máx}$ aumentaram proporcionalmente com a dose oral na faixa de 0,25 a 10 mg/kg, e a biodisponibilidade absoluta em 12 doentes adultos foi de 86% ± 16% (média ± DP) para o comprimido de 150 mg e 87% ± 13% para a solução oral. A ligação da lamivudina às proteínas plasmáticas humanas é baixa (< 36%). Dentro de 12 horas após uma dose oral única de lamivudina em 6 adultos infetados com VIH-1, 5,2% ± 1,4% (média ± DP) da dose foi excretada como metabolito trans-sulfóxido na urina. A maioria da lamivudina é eliminada inalterada na urina por secreção catiónica orgânica ativa, e a semi-vida de eliminação média observada ($t_{1/2}$) variou de 5 a 7 horas na maioria dos estudos de dose única com amostragem de soro durante 24 horas após a administração.

Fumarato de Tenofovir Disoproxil: Após administração oral de uma dose única de 300 mg de fumarato de tenofovir disoproxil em indivíduos infetados com VIH-1 em estado de jejum, as concentrações séricas máximas ($C_{máx}$) foram alcançadas em 1,0 ± 0,4 horas (média ± DP) e os valores de $C_{máx}$ e ASC foram de 296 ± 90 ng/ml e 2287 ± 685 ng•h/ml, respetivamente. A biodisponibilidade oral do tenofovir de fumarato de tenofovir disoproxil em indivíduos em jejum é de aproximadamente 25%. Menos de 0,7% de tenofovir faz ligação a proteínas plasmáticas humanas *in vitro* e a ligação é independente da concentração na faixa de 0,01 a 25 mcg/ml. Aproximadamente 70 a 80% da dose intravenosa de tenofovir é recuperada como medicamento inalterado na urina. O tenofovir é eliminado por uma combinação de filtração glomerular e secreção tubular ativa com depuração renal em adultos com função renal normal de 243 ± 33 ml/min (média ± DP). Após uma dose oral única, a semi-vida de eliminação terminal de tenofovir é de aproximadamente 17 horas.

Populações Especiais: *Raça:* Efavirenz e Lamivudina: Não há diferenças raciais significativas ou clinicamente relevantes na farmacocinética de efavirenz e lamivudina.

Fumarato de Tenofovir Disoproxil: Para além do grupo caucasiano, houve um número de dados insuficiente de outros grupos raciais e étnicos para se poder determinar adequadamente as possíveis diferenças farmacocinéticas entre essas populações.

Género: Não há diferenças de género significativas ou clinicamente relevantes na farmacocinética de efavirenz, lamivudina e fumarato de tenofovir disoproxil.

Doentes Geriátricos: A farmacocinética da lamivudina e do fumarato de tenofovir disoproxil não foi estudada em doentes com mais de 65 anos de idade.

Pediatria: Este comprimido de combinação não deve ser administrado a doentes com peso inferior a 40 kg.

Doentes com Compromisso Renal:[Ver Uso em Populações Específicas (8.6).]

Os comprimidos de efavirenz, lamivudina e fumarato de tenofovir disoproxil não são recomendados para doentes com compromisso renal (ou seja, depuração da creatinina inferior a 50 ml/min) ou com doença renal em fase terminal (ESRD) que requer hemodiálise, porque é uma formulação com combinação em dose fixa que não pode ser ajustada.

Doentes com Insuficiência Hepática: Efavirenz: Um estudo de dose múltipla não mostrou efeito significativo na farmacocinética de efavirenz em doentes com insuficiência hepática leve (Classe A de Child-Pugh) em comparação com os controlos. Não houve dados suficientes para determinar se a insuficiência hepática moderada ou grave (Classe B ou C de Child-Pugh) afeta a farmacocinética do efavirenz.

Lamivudina: As propriedades farmacocinéticas da lamivudina foram determinadas em adultos com insuficiência hepática. Os parâmetros farmacocinéticos não foram alterados pela diminuição da função hepática. A segurança e a eficácia da lamivudina não foram estabelecidas na presença de doença hepática descompensada.

Fumarato de Tenofovir Disoproxil: A farmacocinética do tenofovir após uma dose única de 300 mg de fumarato de tenofovir disoproxil foi estudada em indivíduos não infetados pelo VIH com insuficiência hepática moderada a grave. Não houve alterações substanciais na farmacocinética do tenofovir em indivíduos com insuficiência hepática em comparação com indivíduos não afetados. Não é necessária nenhuma alteração na administração de fumarato de tenofovir disoproxil em doentes com insuficiência hepática.

Avaliação de interações medicamentosas:[Ver Interações Medicamentosas (7).]

Efavirenz: O efavirenz demonstrou *in vivo* causar indução de enzimas hepáticas, aumentando assim a biotransformação de alguns medicamentos metabolizados pela CYP3A e pela CYP2B6. Estudos *in vitro* demonstraram que o efavirenz inibiu as isoenzimas CYP 2C9, 2C19 e 3A4 com valores de K_i (8,5 a 17 µM) nas faixas observadas de concentrações plasmáticas de efavirenz. Em estudos *in vitro*, o efavirenz não inibiu a CYP2E1 e inibiu a CYP2D6 e CYP1A2 (valores de K_i de 82 a 160 µM) apenas em concentrações bem acima das obtidas clinicamente. A coadministração de efavirenz com medicamentos primariamente metabolizados pelas isoenzimas 2C9, 2C19 e 3A pode resultar em concentrações plasmáticas alteradas do medicamento coadministrado. É esperado que os medicamentos que induzem a atividade da CYP3A aumentem a depuração do efavirenz, resultando em baixas concentrações plasmáticas.

Foram realizados estudos de interação medicamentosa com efavirenz e outros fármacos susceptíveis de serem coadministrados ou com medicamentos comumente usados como verificadores da interação farmacocinética. Os efeitos da coadministração de efavirenz na $C_{máx}$, ASC, e $C_{mín}$ estão resumidos na Tabela 4 (efeito do efavirenz noutros medicamentos) e Tabela 5 (efeito de outros medicamentos no efavirenz). Para mais informações sobre recomendações clínicas, ver *Interações Medicamentosas (7.5)*.

Tabela 4. Efeito do Efavirenz na Concentração Plasmática do Medicamento Coadministrado, $C_{máx}$, ASC, e $C_{mín}$

Medicamento Coadministrado	Dose	Dose de Efavirenz	Número de Indivíduos	Medicamento Coadministrado (alteração % média) $C_{máx}$ (90% IC)	ASC (90% IC)	$C_{mín}$ (90% IC)
Boceprevir	800 mg tid x 6 dias	600 mg qd x 16 dias	ND	↓ 8% (↓ 22-↑ 8%)	↓ 19% (11-25%)	↓ 44% (26-58%)
Simeprevir	150 mg qd x 14 dias	600 mg qd x 14 dias	23	↓ 51% (↓ 46-↓ 56%)	↓ 71% (↓ 67-↓ 74%)	↓ 91% (↓ 88-↓ 92%)
Azitromicina	600 mg dose única	400 mg qd x 7 dias	14	↑ 22% (4-42%)	↔	NA
Claritromicina	500 mg q12h x 7 dias	400 mg qd x 7 dias	11	↓ 26% (15-35%)	↓ 39% (30-46%)	↓ 53% (42-63%)
metabolito 14-OH				↓ 49% (32-69%)	↑ 34% (18-53%)	↑ 26% (9-45%)
Fluconazol	200 mg x 7 dias	400 mg qd x 7 dias	10	↔	↔	↔
Itraconazol	200 mg q12h x 28 dias	600 mg qd x 14 dias	18	↓ 37% (20-51%)	↓ 39% (21-53%)	↓ 44% (27-58%)
Hidroxi-itraconazol				↓ 35% (12-52%)	↓ 37% (14-55%)	↓ 43% (18-60%)
Posaconazol	400 mg (suspensão oral) bid x 10 e 20 dias	400 mg qd x 10 e 20 dias	11	↓ 45% (34-53%)	↓ 50% (40-57%)	ND
Rifabutina	300 mg qd x 14 dias	600 mg qd x 14 dias	9	↓ 32% (15-46%)	↓ 38% (28-47%)	↓ 45% (31-56%)
Voriconazol	400 mg po q12h x 1 dia, seguido de 200 mg po q 12h x 8 dias	400 mg qd x 9 dias	ND	↓ 61%[a]	↓ 77%[a]	ND
	300 mg po q12h dias 2-7	300 mg qd x 7 dias	ND	↓ 36%[b] (21-49%)	↓ 55%[b] (45-62%)	ND
	400 mg po q12h dias 2-7	300 mg qd x 7 dias	ND	↑ 23%[b] (↓ 1-↑ 53%)	↓ 7%[b] (↓23-↑13%)	ND
Arteméter/lumefantrina	Arteméter 20 mg / lumefantrina 120 mg, comprimidos (6 doses de 4 comprimidos durante 3 dias)	600 mg qd x 26 dias	12			
Arteméter				↓ 21%	↓ 51%	ND
dihidroartem-isinina				↓ 38%	↓ 46%	ND
lumefantrina				↔	↓ 21%	ND
Atorvastatina	10 mg qd x 4 dias	600 mg qd x 15 dias	14	↓ 14% (1-26%)	↓ 43% (34-50%)	↓ 69% (49-81%)
Total ativo (incluindo metabolitos)				↓ 15% (2-26%)	↓ 32% (21-41%)	↓ 48% (23-64%)
Pravastatina	40 mg qd x 4 dias	600 mg qd x 15 dias	13	↓ 32% (↓ 59-↑ 12%)	↓ 44% (26-57%)	↓ 19% (0-35%)
Sinvastatina	40 mg qd x 4 dias	600 mg qd x 15 dias	14	↓ 72% (63-79%)	↓ 68% (62-73%)	↓ 45% (20-62%)
Total ativo (incluindo metabolitos)				↓ 68% (55-78%)	↓ 60% (52-68%)	ND[c]
CCarbamazepina	200 mg qd x 3 dias, 200 mg bid x 3 dias, seguido de 400 mg qd x 29 dias	600 mg qd x 14 dias	12	↓ 20% (15-24%)	↓ 27% (20-33%)	↓ 35% (24-44%)
Metabolito epóxido				↔	↔	↓ 13% (↓ 30-↑7%)

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Size : 500 x 950 mm
Book Folding : 45 x 60 mm
Color : Black
Spec: Printed on 40 GSM Bible paper, front & back side printing.

Pharma Code : 4646 4647

Note: Pharma code position, Orientation & Product Name Size are tentative, will be change based on folding size

Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets 200/300/300 mg

Rx Only

Revised: 06/2017

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: 2006

WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT ACUTE EXACERBATIONS OF HEPATITIS B
See full prescribing information for complete boxed warning.
- **Lactic acidosis and hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues including lamivudine and tenofovir disoproxil fumarate. (5.1)**
- **Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with HIV-1 and hepatitis B virus and have discontinued FTC, 3TC or TDF, components of EFAVIRENZ, LAMIVUDINE and tenofovir disoproxil fumarate. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.2)**

INDICATIONS AND USAGE
Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, a combination of one non-nucleoside reverse transcriptase inhibitor (efavirenz) and two nucleoside reverse transcriptase inhibitors (lamivudine and tenofovir disoproxil fumarate), are indicated for use alone as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adult patients with no prior antiretroviral use. (1)

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

DOSAGE FORMS AND STRENGTHS
Tablets: 600 mg of efavirenz, 300 mg lamivudine and 300 mg tenofovir disoproxil fumarate. (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. (4.1)

WARNINGS AND PRECAUTIONS
- Coadministration with Other Products: Do not use with other efavirenz, lamivudine or tenofovir-containing products. Do not administer with lamivudine as the only component of a combination product. (5.3)
- Hepatic decompensation, some fatal, has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy and may occur in patients without pre-existing liver disease or other identifiable risk factors. Discontinue efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, as medically appropriate and consider dose reduction or discontinuation of interferon alfa, ribavirin, or both. (5.4)
- Mitochondrial Dysfunction after Exposure in Utero: Nucleoside analogs may cause delayed mitochondrial dysfunction syndromes. Monitor pediatric patients exposed in utero to nucleoside analogs and consider appropriate diagnostic evaluation. (5.5)
- New Onset or Worsening Renal Impairment: Can include acute renal failure and Fanconi syndrome. Assess estimated creatinine clearance before initiating treatment with tenofovir disoproxil fumarate, a component of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. Avoid use of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets with concurrent or recent use of nephrotoxic drugs. (5.6)

FULL PRESCRIBING INFORMATION: CONTENTS*
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2.1 Recommended Dosage for Adult Patients and Pediatric Patients (40 kg or More)
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3 DOSAGE FORMS AND STRENGTHS
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FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT ACUTE EXACERBATIONS OF HEPATITIS B

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

Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and HIV-1 and have discontinued FTC, 3TC or TDF, components of efavirenz, lamivudine and tenofovir disoproxil fumarate. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment *(see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

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

The recommended dosage of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets is 600 mg/300 mg/300 mg orally, once daily. It is recommended that efavirenz, lamivudine and tenofovir disoproxil fumarate tablets be taken on an empty stomach, preferably at bedtime. Administration with food may result in increased efavirenz exposure and increased adverse reactions *(see Clinical Pharmacology and Pharmacokinetics (12.3), Adverse Reactions (6.1) and Patient Counseling Information (17)]*. Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should be swallowed intact with liquid.

2.2 Dose Adjustment for Renal Impairment

Because efavirenz, lamivudine and tenofovir disoproxil fumarate is a fixed-dose combination tablet, it is not recommended for patients with estimated creatinine clearance less than 50 mL/min or pediatric patients and end-stage renal disease (ESRD) requiring hemodialysis.

3 DOSAGE FORMS AND STRENGTHS

Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets are available containing 600 mg of efavirenz, 300 mg of lamivudine, USP and 300 mg tenofovir disoproxil fumarate equivalent to 245 mg of tenofovir disoproxil.

- The 600 mg/300 mg/300 mg tablets are yellow colored, capsule-shaped, bevel edged biconvex film coated tablets debossed with "1" on one side and "227" on the other side.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are contraindicated in patients with a previous hypersensitivity reaction to any of the components contained in the formulation.

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis/Severe Hepatomegaly With Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues including lamivudine and tenofovir. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Caution should be exercised when administering any nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase increases).

5.2 Patients Coinfected with HIV-1 and HBV

It is recommended that all patients with HIV-1 be tested for the presence of chronic hepatitis B virus (HBV) before initiating antiretroviral therapy. Discontinuation of anti-HBV therapy, including lamivudine and tenofovir disoproxil fumarate, may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted.

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

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

5.3 Coadministration with Other Products

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are a fixed-dose combination product of efavirenz, lamivudine and tenofovir disoproxil fumarate. Do not administer efavirenz, lamivudine and tenofovir disoproxil fumarate (including lamivudine-containing, or emtricitabine-containing drugs), emtricitabine (Emtriva®, Coviracil®), EPIVIR® or EPIVIR-HBV® (lamivudine), EPZICOM® (abacavir sulfate/lamivudine), TRIZIVIR® (abacavir sulfate/lamivudine/zidovudine), METHADOSE® (methadone), SUSTIVA® (efavirenz) or delavirdine mesylate, VIREAD® (tenofovir disoproxil fumarate), ATRIPLA® (emtricitabine/efavirenz/tenofovir disoproxil fumarate), COMBIVIR® (lamivudine/zidovudine), or EMTRIVA® (emtricitabine) with efavirenz, lamivudine and tenofovir disoproxil fumarate tablets.

Tenofovir disoproxil fumarate and lamivudine should not be administered in combination with HEPSERA® (adefovir dipivoxil) *(see Drug Interactions (7.2)]*.

5.4 Use With Interferon- and Ribavirin-Based Regimens

In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine, a component of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. Although no evidence of an interaction between ribavirin and efavirenz, lamivudine or tenofovir has been observed, caution should be exercised when ribavirin was coadministered with lamivudine or HIV-1/HCV co-infected patients *[see Clinical Pharmacology (12.3)]* hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy and may occur in patients without pre-existing liver disease or other identifiable risk factors. Discontinuation of efavirenz with ribavirin, or both should also be considered if worsening clinical hepatic decompensation. Discontinuation of lamivudine should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Child-Pugh-c). See the full prescribing information for interferon and ribavirin.

5.5 Pancreatitis

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

5.6 New Onset or Worsening Renal Impairment

Tenofovir, a component of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets is principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir disoproxil fumarate *[see Clinical Pharmacology (12.3)]*.

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

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should be avoided with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs)) *[see Drug Interactions (7.2)]*. Cases of acute renal failure after initiation of high-dose or multiple NSAIDs have been reported in HIV-infected patients with risk factors for renal dysfunction who appeared stable on tenofovir disoproxil fumarate. Some patients required hospitalization and renal replacement therapy. Alternatives to NSAIDs should be considered, if needed, in patients at risk for renal dysfunction.

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

5.7 Psychiatric Symptoms

Serious psychiatric adverse experiences have been reported in patients treated with efavirenz, a component of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. In controlled trials of 1008 patients treated with regimens containing efavirenz for a mean of 2.1 years and 635 patients treated with control regimens for a mean of 1.5 years, the frequency (regardless of causality) of specific serious psychiatric events among patients exposed efavirenz or control regimens, respectively, were severe depression (2.4%, 0.9%), suicidal ideation (0.7%, 0.3%), nonaggressive hostility directed at others (0.4%, 0.3%), severe manic reactions (0.4%, 0.3%), and severe psychotic reactions (0.8%, 0.3%). When psychiatric symptoms similar to those noted above were considered, or evaluated as a group in a multifactorial analysis of data from Study 006, treatment with efavirenz was associated with a 2- to 3-fold higher risk of these symptoms relative to control. Some of these symptoms appeared to contribute to the occurrence of these psychiatric symptoms were history of injection drug use, psychiatric history, and receipt of psychiatric medication at study entry; similar associations were observed in both the efavirenz and control treatment groups. In Study 006, short of new serious psychiatric symptoms occurred throughout the study for both efavirenz-treated and control-treated patients. One percent of efavirenz-treated patients discontinued therapy.

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, and catatonia, although a causal relationship to the use of efavirenz cannot be determined from these reports. Patients with serious psychiatric adverse experiences should seek immediate medical evaluation to assess the possibility of suicidality, to establish the diagnosis and identify the role, if any, of efavirenz, and to institute appropriate treatment. Discontinuation of treatment should be considered.

5.8 Nervous System Symptoms

Fifty-three percent (531/1008) of patients receiving efavirenz, a component of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, in controlled trials reported central nervous system symptoms (any grade, regardless of causality) compared to 26% (135/510) of patients receiving control regimens. These symptoms included, but were not limited to, dizziness (9.1% of the 1008 patients), insomnia (8.3%), impaired concentration (6.2%), somnolence (5.2%), and abnormal dreams or vivid dreams (4.2%). Moderate to severe dizziness was seen in 2.7% of patients and 0.4% of patients discontinued therapy as a result. These symptoms usually began 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 frequency of these symptoms was similar to that seen in control-treated patients. In Study 006, 19% of patients treated with efavirenz-containing regimens and 2% to 5% in patients treated with control regimens reported these symptoms. Patients should be informed that these common symptoms were likely to improve with continued therapy and were not predictive of subsequent onset of the less frequent psychiatric symptoms *(see Warnings and Precautions (5.7)]*. Dosing of bedtime may improve the tolerability of these nervous system symptoms *(see Dosage and Administration (2.1)]*.

Analysis of long-term data from Study 006 (median follow-up 180 weeks, 100 weeks, and 36 weeks for patients treated with efavirenz + lamivudine + stavudine, efavirenz + indinavir, and indinavir + zidovudine + lamivudine, respectively) showed that, beyond the first 4 weeks of therapy, the incidences of new nervous system symptoms among efavirenz-treated patients were generally similar to those in the indinavir-containing control arm.

Efavirenz has a prolonged half-life (40 to 55 hours). Patients should be informed that dizziness or impaired concentration may occur for an unpredictable period of time. Caution should be exercised when administering efavirenz to patients who operate potentially hazardous machinery, including motor vehicles or heavy equipment.

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

5.9 Embryo-Fetal Toxicity

Efavirenz, a component of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, may cause fetal harm when administered during the first trimester to a pregnant woman. Advise females of reproductive potential who are receiving efavirenz to avoid pregnancy. *(See Use in Specific Populations (8.1).)*

5.10 Rash

In controlled clinical trials, 26% (266/1008) of patients treated with 600 mg efavirenz experienced new-onset skin rash compared with 17% (117/682) of patients treated in control groups. Rash associated with blistering, moist desquamation, or ulceration occurred in 0.9% (9/1008) of patients treated with efavirenz. The majority of cases of rash (a majority of mild to moderate macular papular rash with pruritus) occurred during the first 2 weeks of therapy and resolved spontaneously with continued dosing; the median time to resolution was 29 days. Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first 2 weeks of therapy. Efavirenz may be restarted following mild to moderate rash. In clinical trials, in most patients continuing therapy with efavirenz, rash resolves within 1 month (median 16 days). The discontinuation rate for rash in clinical trials was 1.7% (17/1008).

Efavirenz can generally be reinitiated in patients interrupting therapy because of rash. Efavirenz should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement, or fever. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash. For patients who have had a life-threatening cutaneous reaction (e.g., Stevens-Johnson syndrome), alternative therapy should be considered. *(see Contraindications (4.1))*.

Rash was reported in 5% of 3 hundred and seventy (48/1) treated with efavirenz regimens; patients experienced Grade 3 rash (confluent rash with fever), and two patients had Grade 4 rash (erythema multiforme). The median time to onset of rash in pediatric patients was 8 days. Prophylaxis with appropriate antihistamine before initiating therapy with efavirenz in pediatric patients should be considered.

5.11 Hepatotoxicity

Monitoring of liver enzymes before and during treatment is recommended for patients with underlying hepatic disease, including chronic hepatitis B or C infection, or in patients who have marked elevations of liver enzymes or with other medications associated with liver toxicity *(see Use in Specific Populations (8.6))*. A few of these postmarketing reports of hepatic failure occurred in patients with no pre-existing hepatic disease or other identifiable risk factors. Fatal cases have been reported in patients with pre-existing liver disease or cirrhosis. Patients with pre-existing hepatic dysfunction or chronic liver infections, or patients with persistent elevations of serum transaminases to greater than five times the upper limit of the normal range, the benefit of continued therapy with efavirenz needs to be weighed against the potential risks of significant liver toxicity.

5.12 Convulsions

Convulsions have been observed in patients receiving efavirenz, generally in the presence of known medical history of seizures *[see Nonclinical Toxicology (13.2)]*. Caution should be taken in any patient with a history of seizures. These patients should be monitored during treatment with efavirenz. Concomitant medications may also alter the plasma levels of phenytoin and phenobarbital. If possible, these agents should be avoided during treatment with efavirenz.

5.13 Lipid Elevations

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

5.14 Bone Effects

Bone Mineral Density: In clinical trials in HIV-1 infected adults, tenofovir disoproxil fumarate was associated with slightly greater decreases in bone mineral density (BMD) and increases in biochemical markers of bone metabolism, indicative of bone turnover, than comparators. These changes in bone mineral density were not associated with increased bone pain or fractures in clinical trials. Decreases in BMD and increases in biochemical markers of bone turnover were similar in patients receiving tenofovir disoproxil fumarate or stavudine.

Clinical trials evaluating tenofovir disoproxil fumarate in pediatric and adolescent subjects were conducted. Under normal circumstances, BMD increases rapidly in pediatric patients. In HIV-1 infected subjects aged 2 years to less than 18 years, bone effects were similar to those observed in adult subjects and suggest increased bone turnover. In this population, there was a greater effect on height z-score and greater increases in BMD in the tenofovir disoproxil fumarate group compared to the control group. Similar trends were observed in chronic hepatitis B infected subjects between the aged 12 years to less than 18 years. In all pediatric trials, skeletal growth (defined as height and weight) was evaluated. There was no evidence of clinically significant abnormalities of skeletal growth.

Effects of tenofovir disoproxil fumarate-associated changes in BMD and biochemical markers on long-term bone health are unknown. Assessment of BMD should be considered for adults and pediatric patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained.

Osteonecrosis/Avascular Necrosis: Cases of osteonecrosis associated with proximal renal tubulopathy, manifested as bone pain or pain in extremities and which may contribute to fracture, have been reported in association with the use of tenofovir disoproxil fumarate. Osteonecrosis is multifactorial in etiology, and the relative contribution of tenofovir disoproxil fumarate is unknown. Appropriate diagnostic and therapeutic measures should be instituted as clinically indicated. Patients should be considered at risk of renal dysfunction who present with persistent or worsening bone pain, pain in extremities, fractures and/or muscular pain or weakness *(see Warnings and Precautions (5.6))*.

5.15 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in HIV-infected patients treated with coordination antiretroviral therapy, including efavirenz, lamivudine and tenofovir disoproxil fumarate. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond 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) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment.

5.16 Fat Redistribution

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

5.17 GI Prokinetics

GI prokinetics has been observed with the use of efavirenz *[see Drug Interactions (7.2, 7.6) and Clinical Pharmacology (12.3)]*. Consider alternatives to efavirenz when coadministered with a drug with a known risk of Torsade de Pointes or when administered to patients at higher risk of Torsade de Pointes.

6 ADVERSE REACTIONS

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

- Lactic Acidosis/Severe Hepatomegaly with Steatosis *[see Boxed Warning, Warnings and Precautions (5.1)]*.
- Exacerbations of Hepatitis B *[see Boxed Warning, Warnings and Precautions (5.2)]*.
- Hepatic Decompensation in Patients Co-infected with HIV-1 and Hepatitis C *[see Warnings and Precautions (5.4)]*.
- Pancreatitis *[see Warnings and Precautions (5.5)]*.
- New Onset or Worsening Renal Impairment *[see Warnings and Precautions (5.6)]*.
- Psychiatric Symptoms *[see Warnings and Precautions (5.7)]*.
- Nervous System Symptoms *[see Warnings and Precautions (5.8)]*.
- Rash *[see Warnings and Precautions (5.10)]*.
- Hepatotoxicity *[see Warnings and Precautions (5.11)]*.
- Convulsions *[see Warnings and Precautions (5.12)]*.
- Lipid Elevations *[see Warnings and Precautions (5.13)]*.
- Bone Effects *[see Warnings and Precautions (5.14)]*.
- Immune Reconstitution Syndrome *[see Warnings and Precautions (5.15)]*.
- Fat Redistribution *[see Warnings and Precautions (5.16)]*.

6.1 Clinical Trials Experience

Clinical Trials Experience in Adult Patients with HIV-1 Infection

- Lactic Acidosis/Severe Hepatomegaly with Steatosis *[see Boxed Warning, Warnings and Precautions (5.1)]*.
- Exacerbations of Hepatitis B *[see Boxed Warning, Warnings and Precautions (5.2)]*.
- Hepatic Decompensation in Patients Co-infected with HIV-1 and Hepatitis C *[see Warnings and Precautions (5.4)]*.
- Pancreatitis *[see Warnings and Precautions (5.5)]*.
- New Onset or Worsening Renal Impairment *[see Warnings and Precautions (5.6)]*.
- Psychiatric Symptoms *[see Warnings and Precautions (5.7)]*.
- Nervous System Symptoms *[see Warnings and Precautions (5.8)]*.
- Rash *[see Warnings and Precautions (5.10)]*.
- Hepatotoxicity *[see Warnings and Precautions (5.11)]*.
- Convulsions *[see Warnings and Precautions (5.12)]*.
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- Immune Reconstitution Syndrome *[see Warnings and Precautions (5.15)]*.
- Fat Redistribution *[see Warnings and Precautions (5.16)]*.

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- Convulsions *[see Warnings and Precautions (5.12)]*.
- Lipid Elevations *[see Warnings and Precautions (5.13)]*.
- Bone Effects *[see Warnings and Precautions (5.14)]*.
- Immune Reconstitution Syndrome *[see Warnings and Precautions (5.15)]*.
- Fat Redistribution *[see Warnings and Precautions (5.16)]*.

- The interaction between efavirenz and the drug was evaluated in a clinical study. All other drug interactions observed are class interactions.

7 DRUG INTERACTIONS

7.6 Drugs without Clinically Significant Interactions

No clinically significant drug interactions have been observed when lamivudine, tenofovir disoproxil fumarate tablets are coadministered with the following: aluminum/magnesium hydroxide antacids, azithromycin, cetirizine, famotidine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Efavirenz:

Risk Summary. There are retrospective case reports of neural tube defects in infants whose mothers were exposed to efavirenz-containing regimens in the first trimester of pregnancy. Prospective pregnancy data from the Antiretroviral Pregnancy Registry (APR) are insufficient to evaluate the risk of neural tube defects following exposure to efavirenz during the first trimester of human pregnancy. Efavirenz should not be used in the first trimester of pregnancy. Advise pregnant women of the potential risk to the fetus.

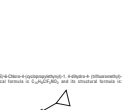
Data: Human Data: There are retrospective postmarketing reports of findings consistent with neural tube defects, including myelomeningocele, in infants whose mothers were exposed to efavirenz during the first trimester of pregnancy. Based on prospective reports to the APR of 766 exposed pregnancies (live births, stillbirths, or elective terminations following exposure to efavirenz-containing regimens (including over 600 live births exposed in the first trimester), there was no difference between the overall birth defect rate for efavirenz compared with the background birth defect rate of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program. As of the reporting date of the APR, there were 19 prospectively reported cases of neural tube defects following first trimester exposure to efavirenz (2.5% [19/766]). The observed prevalence of neural tube defects in these cases is higher than the background rate of neural tube defect. A single case of anophthalmia with first-trimester exposure to efavirenz has also been prospectively reported to the APR. Neural tube defects, including anencephaly and myelomeningocele, have been observed in animal studies *[see Nonclinical Toxicology (13.1)]*.

Animal Data: Effects of efavirenz on embryo-fetal development have been studied in three nonclinical species (mouse, rat, and rabbit). Efavirenz was teratogenic in mice at exposures 0.2 times the exposure in humans at the recommended dose of 600 mg. Lamivudine was not teratogenic in mice at clinically relevant exposures, but *in vivo* effects on embryo-fetal development were observed only at exposures sufficiently in excess of human exposures to be of little clinical significance. Efavirenz was not teratogenic in rats at exposures 17 times the exposure in humans at the recommended dose of 600 mg, but was embryocidal at exposures 0.9 times the exposure in humans at the recommended dose. Efavirenz was not teratogenic in rabbits at exposures 0.3 times the exposure in humans at the recommended dose of 600 mg. Lamivudine was not teratogenic in rabbits at clinically relevant exposures, but was embryocidal at exposures sufficiently in excess of human exposures to be of little clinical significance. Tenofovir disoproxil fumarate was not teratogenic in mice and rats at exposures 2 and 6 times, respectively, the human exposure at the recommended dose of 300 mg, but was embryocidal at these exposures in rats. Tenofovir disoproxil fumarate was not teratogenic in rabbits at exposures 0.3 times the human exposure at the recommended dose of 300 mg, but was embryocidal at this exposure in rabbits.

Lamivudine:

Risk Summary. Available data from an ERS, a synthetic nucleoside analogue with activity against HIV-1 and HBV. The molecular formula is $C_8H_{11}N_3O_3S$ and the molecular weight of 229.26. It is a white to off-white crystalline powder.

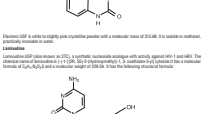
Lamivudine



Lamivudine USP is an off – white solid. It is soluble in water.

Tenofovir disoproxil fumarate

Tenofovir disoproxil fumarate is a nucleotide analog reverse transcriptase inhibitor and an HBV reverse transcriptase inhibitor. Tenofovir disoproxil fumarate is a fumaric acid salt of a diester prodrug of tenofovir, which is converted to tenofovir by cellular and viral esterases. The chemical name of tenofovir disoproxil fumarate is [(*R*)-9- [(*R*)- 2- [bis [(isopropoxy-carbonyloxy) methoxy] phosphinyl] propyl] adenine fumarate (1:1) salt. The molecular formula of tenofovir disoproxil fumarate is $C_{19}H_{30}N_5O_{10}P \cdot C_4H_4O_4$ and a molecular weight of 635.52. It is a white to off-white powder.



Tenofovir disoproxil fumarate is a white crystalline powder which is sparingly soluble in methanol and in ethanol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are a fixed-dose combination of antiviral drugs with activity against HIV-1 *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Cardiac Electrophysiology: The effect of efavirenz on the QTc interval was evaluated in an open-label, positive- and placebo-controlled, crossover study in 39 healthy adult subjects who received a single dose of efavirenz 400 mg, moxifloxacin 400 mg (a positive control), and placebo. The mean (90% CI) placebo-adjusted change from baseline in QTcF (Fridericia correction) following the administration of 400 mg daily dose for 7 days was 3.26-fold the mean C_{max} observed in subjects receiving 600 mg daily dose of efavirenz. No subject experienced a change from baseline QTcF > 500 msec. The effect of efavirenz on the mean corrected QT interval was similar on Day 1 and Day 7, indicating that no accumulation occurred.

Viral Dynamics: Following oral administration of a single 600 mg dose of efavirenz to HIV-1 infected subjects, efavirenz plasma concentrations were characterized by a median T_{max} of 5 hours and a mean terminal half-life of 52 to 76 hours. Steady-state plasma concentrations were reached within 6 to 10 days. In 35 HIV-1 infected subjects receiving efavirenz 600 mg once daily for 14 days, the mean (± SD) C_{max} was 4.3 (± 1.1) µM and AUC was 58.1 (± 17.3) µM • hr. Efavirenz is highly bound (approximately 99.5 to 99.75%) to human plasma proteins, predominantly albumin. Efavirenz is metabolized by CYP450 enzymes to primarily hydroxylated metabolites which undergo subsequent glucuronidation before excretion. The primary enzyme responsible for efavirenz metabolism is CYP2B6. CYP3A4 and CYP2A6 are the major enzymes responsible for efavirenz metabolism. Efavirenz has been shown to induce CYP3A4 and CYP2B6 enzymes, which may result in increased metabolism of these substrates. In 47 HIV-1 infected subjects given efavirenz 600 mg once daily for 10 days, approximately 14 to 69% 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 mean renal clearance of 210 to 307 mL/min (more than creatinine clearance) following a single oral dose, the terminal elimination half-life of tenofovir is approximately 17 hours.

Special Populations: Hepatic Impairment: There was no significant or clinically relevant racial difference in efavirenz and tenofovir plasma pharmacokinetics.

Renal Impairment: Efavirenz pharmacokinetics have not been studied in patients with renal impairment.

Gender: There are no significant or clinically relevant gender differences in the pharmacokinetics of efavirenz, lamivudine, and tenofovir disoproxil fumarate.

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

Pediatric: The combination tablet should not be administered to patients weighing less than 40 kg.

Patients with Hepatitis B and/or Hepatitis C Virus Co-infection:

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

Lamivudine: After oral administration of 2 mg/kg of lamivudine twice a day to 8 adults with HIV-1, the peak serum concentration (C_{max}) was 2.2 ± 0.8 µg/mL (mean ± SD), and the area under the plasma concentration-time curve (AUC) and C_{max} increased in proportion to oral dose over the range from 0.5 to 10 mg/kg (the clinical dose is 4 mg/kg). The absolute bioavailability of oral dose was 86 ± 16% (mean ± SD). Less than 10% to the oral solution. Binding of lamivudine to human plasma proteins is low (< 36%). Within 12 hours after a single oral dose of lamivudine to 6 HIV-1 infected adults, 5.2% ± 1.4% (mean ± SD) of the dose was excreted as the trans-sulfoxide metabolite in the urine. The majority of lamivudine is eliminated unchanged in urine by organic cationic secretion and the observed mean elimination half-life ($t_{1/2}$) ranged from 5 to 7 hours in most clinical studies of patients with normal renal function.

Tenofovir Disoproxil Fumarate: Following oral administration of a single 300 mg dose of tenofovir disoproxil fumarate to HIV-1 infected subjects, tenofovir dis

POINTS SAILLANTS DES RENSEIGNEMENTS THÉRAPEUTIQUES

Ces faits saillants ne comprennent pas toutes les informations nécessaires pour utiliser ÉFAVIRENZ, LAMIVUDINE ET FUMARATE DE TÉNOFOVIR DISOPROXIL COMPRIMÉS de manière sûre et efficace. Voir tous les renseignements thérapeutiques pour ÉFAVIRENZ, LAMIVUDINE ET FUMARATE DE TÉNOFOVIR DISOPROXIL COMPRIMÉS.

ÉFAVIRENZ, LAMIVUDINE et FUMARATE DE TÉNOFOVIR DISOPROXIL comprimés, pour utilisation par voie orale

POM | Schedule: S2 | NS2 | PP

MISES EN GARDE : ACIDOSE LACTIQUE / HÉPATOMÉGALIE SÉVÈRE AVEC STÉATOSE et TRAITEMENT ULTÉRIEUR DES EXACERBATIONS AIGUËS DE L'HÉPATITE B

Voir toutes les renseignements thérapeutiques pour toutes les mises en garde.

- **Une acidose lactique et une hépatomégalie avec stéatose, y compris des cas mortels, ont été rapportés avec l'utilisation d'analogues nucléosidiques, y compris la lamivudine et le fumarate de ténofovir disoproxil. (5.1)**
- **Des exacerbations aigües sévères de l'hépatite B ont été rapportées chez des patients qui sont co-infectés par le virus de l'hépatite B (VHB) et le virus de l'immunodéficience humaine (VIH-1) et qui ont arrêté la lamivudine et le fumarate de ténofovir disoproxil. Surveiller la fonction hépatique de près chez ces patients et, le cas échéant, initier un traitement contre l'hépatite B. (5.2)**

INDICATIONS ET UTILISATIONS

Éfavirenz, lamivudine et fumarate de ténofovir disoproxil comprimés, une combinaison d'un inhibiteur non nucléosidique de la transcriptase inverse (éfavirenz) et de deux inhibiteurs nucléos(t) idiques de la transcriptase inverse (lamivudine et fumarate de ténofovir disoproxil), est destiné à être utilisé seul dans le cadre d'un schéma thérapeutique complet pour le traitement de l'infection par le virus de l'immunodéficience humaine de type 1 (VIH-1) chez les patients adultes et pédiatriques pesant au moins 40 kg. (1)

POSOLOGIE ET ADMINISTRATION

- Dose recommandée : Un comprimé (contenant 600 mg d'éfavirenz, 300 mg de lamivudine et 300 mg de fumarate de ténofovir disoproxil) administré une fois par jour sur un estomac vide, préférablement au coucher. (2.1)

FORMES POSOLOGIQUES ET CONCENTRATIONS

Comprimés : 600 mg d'éfavirenz, 300 mg de lamivudine et 300 mg de fumarate de ténofovir disoproxil. (3)

CONTRE-INDICATIONS

- Éfavirenz, lamivudine et fumarate de ténofovir disoproxil comprimés est contre-indiqué chez les patients présentant une hypersensibilité antérieure (p.ex. syndrome de Stevens-Johnson, érythème polymorphe ou éruption cutanée toxique) à l'un des composants de ce produit. (4.1)

MISES EN GARDE ET PRÉCAUTIONS

- Co-administration avec d'autres produits : Ne pas utiliser avec d'autres produits contenant de l'éfavirenz, de la lamivudine ou du ténofovir ou avec des produits contenant de l'emtricitabine. Ne pas administrer combinaison avec de l'adéfovir dipivoxil. (5.3)
- Une décompensation hépatique, parfois fatale, s'est produite chez des patients co-infectés par le VIH-1 / VHC recevant une thérapie antirétrovirale combinée et des schémas thérapeutiques à base d'interféron et de ribavirine. Surveiller les toxicités associées au traitement. Interrompre éfavirenz, lamivudine et fumarate de ténofovir comprimés, comme médicalement approprié, et envisager une réduction posologique ou l'arrêt de l'interféron alfa, de la ribavirine ou les deux médicaments. (5.4)
- Pancréatite : Utiliser avec prudence chez les patients pédiatriques présentant des antécédents de pancréatite ou d'autres facteurs de risque significatifs de pancréatite. Arrêter éfavirenz, lamivudine et fumarate de ténofovir disoproxil comprimés comme cliniquement approprié. (5.5)
- Nouveau début ou aggravation d'insuffisance rénale : Peut comprendre une insuffisance rénale aiguë et le syndrome de Fanconi. Évaluer la clairance estimée de la créatinine avant d'initier le traitement avec le fumarate de ténofovir disoproxil, un composant d'éfavirenz, lamivudine et fumarate de ténofovir disoproxil comprimés. Chez les patients à risque de dysfonctionnement rénale, évaluer la clairance de la créatinine estimée, le phosphore sérique, la glucose urinaire et les protéines urinaires avant d'initier le traitement par ténofovir et périodiquement pendant le traitement. Éviter l'administration d'éfivarenz, lamivudine et fumarate de ténofovir disoproxil comprimés avec l'utilisation concomitante ou récente de médicaments néphrotoxiques. (5.6)
- Symptômes psychiatriques graves :Une évaluation médicale immédiate est recommandée pour les symptômes psychiatriques graves tels que la dépression sévère ou les idées suicidaires. (5.7, 17)
- Symptômes du Système Nerveux (SSN) : Les SSN sont fréquents, commencent généralement 1 à 2 jours après l'initiation de la thérapie et se résolvent en 2 à 4 semaines. L'administration de la dose au coucher peut améliorer la tolérance. Les SSN ne prédisent pas l'apparition de symptômes psychiatriques. (5.8, 17)
- Toxicité embryo-fœtal : Éviter l'administration pendant le premier trimestre de la grossesse car cela peut causer des dommages au fœtus. (5.9, 8.1)
- Hépatotoxicité :Surveiller les tests de la fonction hépatique avant et pendant le traitement chez les patients présentant une maladie hépatique sous-jacente, y compris la co-infection par l'hépatite B ou C, des élévations marquées des taux de transaminases, ou chez les personnes qui prennent des médicaments associés à une toxicité hépatique. Parmi les cas rapportés d'échec hépatique, quelques-uns se sont produits chez des patients ne présentant pas de maladie hépatique préexistante. (5.11, 8.7)
- Éruption cutanée :L'éruption cutanée se produit habituellement 1 à 2 semaines après l'initiation de la thérapie et se résout dans les 4 semaines. Arrêter la thérapie si une éruption cutanée grave se développe. (5.10, 17)
- Convulsions :Utiliser avec prudence chez les patients présentant des antécédents de crises. (5.12)
- Lipides :Élévations totales des taux de cholestérol et de triglycérides. Surveiller avant la thérapie et périodiquement par la suite. (5.13)
- Diminution de la densité minérale osseuse (DMO) : Observée chez des patients infectés par le VIH. Envisager l'évaluation de la DMO chez les patients présentant des antécédents de fracture pathologique ou d'autres facteurs pour un risque d'ostéoporose ou de perte osseuse. (5.14)
- Syndrome de reconstitution immunitaire : Observé chez des patients infectés par le VIH. Peut nécessiter une évaluation et un traitement ultérieur. (5.15)
- Redistribution / accumulation de graisse corporelle : Observé chez des patients infectés par le VIH recevant une thérapie antirétrovirale combinée. (5.16)

EFFETS INDÉSIRABLES

- Les effets indésirables les plus fréquents sont les troubles de concentration, les rêves anormaux, les maux de tête, les nausées, les malaises et la fatigue, les signes et les symptômes nasaux, les diarrhées, les éruptions cutanées, les étourdissements, l'insomnie, les douleurs, la dépression, l'asthénie et la toux. (6)

INTÉRACTIONS MÉDICAMENTEUSES

La co-administration d'éfavirenz, lamivudine et fumarate de ténofovir disoproxil comprimés peut modifée les concentrations des autres médicaments et les autres médicaments peuvent modifiés la concentration d'éfavirenz, lamivudine et fumarate de ténofovir disoproxil comprimés. Le potentiel d'interactions médicamenteuses doit être envisagé avant et pendant la thérapie. (7)

UTILISATION DANS LES POPULATIONS PARTICULIÈRES

- Grossesse :Les femmes doivent éviter de tomber enceinte pendant le traitement par éfavirenz, un composé d'éfavirenz, lamivudine et fumarate de ténofovir disoproxil comprimés, et pendant 12 semaines après l'arrêt du traitement. (5.9)
- Allaitement :L'allaitement est déconseillé. (8.2)
- Femmes et hommes présentant un potentiel reproductif : Les tests de grossesse et les contraceptions sont recommandés. (8.3)
- Insuffisance hépatique : Éfavirenz est déconseillé chez les patients présentant une insuffisance hépatique modérée ou sévère. Utiliser avec prudence chez les patients présentant une insuffisance hépatique légère. (8.7)
- Patients pédiatriques : L'incidence des éruptions cutanées était plus élevée que chez les adultes. (5.10, 6.1, 8.4)

Voir rubrique 17 pour les RENSEIGNEMENTS SUR LES CONSEILS À DONNER AUX PATIENTS et le feuillet destiné aux patients approuvé par la FDA.

Révisé : 06/2017

RENSEIGNEMENTS THÉRAPEUTIQUES COMPLETS : CONTENU*

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* les rubriques ou les sous-rubriques omises des renseignements thérapeutiques complets ne sont pas listées.

RENSEIGNEMENTS THÉRAPEUTIQUES COMPLETS

MISES EN GARDE : ACIDOSE LACTIQUE / HÉPATOMÉGALIE SÉVÈRE AVEC STÉATOSE et TRAITEMENT ULTÉRIEUR DES EXACERBATIONS AIGUËS DE L'HÉPATITE B

Une acidose lactique et une hépatomégalie avec stéatose, y compris des cas mortels, ont été rapportés avec l'utilisation d'analogues nucléosidiques, y compris la lamivudine et le fumarate de ténofovir disoproxil. Suspendre le traitement si des résultats cliniques ou de laboratoire suggérant une acidose lactique ou une hépatotoxicité prononcée se produisent [voir Mises en garde et Précautions (5.1)]. Des exacerbations aigües sévères de l'hépatite B ont été rapportées chez des patients qui sont co-infectés par le virus de l'hépatite B (VHB) et le virus de l'immunodéficience humaine (VIH-1) et qui ont arrêté la lamivudine et le fumarate de ténofovir disoproxil. Surveiller la fonction hépatique de près chez ces patients et, le cas échéant, initier un traitement contre l'hépatite B *[voir Mises en garde et Précautions (5.2)]*.

1 INDICATIONS ET UTILISATIONS

Éfavirenz, lamivudine et fumarate de ténofovir disoproxil comprimés est destiné à être utilisé seul dans le cadre d'un schéma thérapeutique complet pour le traitement de l'infection par le virus de l'immunodéficience humaine de type 1 (VIH-1) chez les patients adultes et pédiatriques pesant au moins 40 kg.

2 POSOLOGIE ET ADMINISTRATION

2.1 Posologie recommandée chez les patients adultes et pédiatriques pesant au moins 40 kg

La posologie recommandée d'éfavirenz, lamivudine et fumarate de ténofovir disoproxil comprimés est de 600 mg / 300 mg / 300 mg une fois par jour par voie orale. Il est recommandé qu'éfavirenz, lamivudine et fumarate de ténofovir disoproxil comprimés soit administré sur un estomac vide, préférablement au coucher. L'administration de la dose au coucher peut améliorer la tolérance des symptômes du système nerveux *[voir Mises en garde et Précautions (5.7), Effets indésirables (6.1),* et *Renseignements sur les conseils à donner aux patients (17)]*. Éfavirenz, lamivudine et fumarate de ténofovir disoproxil comprimés doit être avaler intact avec du liquide.

2.2 Ajustement posologique pour l'insuffisance rénale

Étant donné qu'éfavirenz, lamivudine et fumarate de ténofovir disoproxil comprimés est un comprimé de combinaison à dose fixe, il est déconseillé chez les patients présentant une insuffisance rénale (clairance de la créatinine inférieure à 50 ml/min) ou chez les patients atteints d'une insuffisance rénale au stade terminal (IRST) nécessitant une hémodialyse.

3 FORMES POSOLOGIQUES ET CONCENTRATIONS

Éfavirenz, Lamivudine et Fumarate de Ténofovir Disoproxil Comprimés est disponible sous forme de comprimés contenant 600 mg d'éfavirenz, USP, 300 mg de lamivudine, USP et 300 mg de fumarate de ténofovir disoproxil équivalent à 245 mg de ténofovir disoproxil.

- Les comprimés de 600 mg / 300 mg / 300 mg sont des comprimés pelliculés biconvexes jaunes en forme de capsule avec des bords biseautés portant la marque 'I' d'un côté et '127' de l'autre.

4 CONTRE-INDICATIONS

4.1 Hypersensibilité

Éfavirenz, lamivudine et fumarate de ténofovir disoproxil comprimés sont contre-indiqués chez les patients présentant une réaction d'hypersensibilité antérieure à l'un des composants contenus dans la formulation.

5 MISES EN GARDE ET PRÉCAUTIONS

5.1 Acidose lactique / hépatomégalie sévère avec stéatose

Une acidose lactique et une hépatomégalie sévère avec stéatose, y compris des cas mortels, ont été rapportés avec l'utilisation d'analogues nucléosidiques et d'autres antirétroviraux. Une majorité de ces cas ont été chez des femmes. L'obésité et l'exposition prolongée à un nucléoside peuvent être des facteurs de risque. Il faut faire preuve de prudence lors de l'administration d'analogues nucléosidiques chez un patient présentant des facteurs de risque connus pour la maladie du foie ; cependant, des cas ont également été rapportés chez des patients qui ne présentaient aucun facteur de risque connu. Le traitement doit être suspendu chez tout patient qui développe des signes cliniques ou de laboratoire suggérant une acidose lactique ou une hépatotoxicité prononcée (qui peut comprendre une hépatomégalie et une stéatose même en l'absence d'élévations marquées des concentrations de transaminases).

5.2 Patients co-infectés par le VIH-1 et le VHB

Il est recommandé que tous les patients atteints par le VIH-1 soient testés pour la présence du virus de l'hépatite B (HBV) chronique avant d'initier la thérapie antirétrovirale. L'arrêt de la thérapie anti-VHB, y compris la lamivudine et le fumarate de ténofovir disoproxil, peut être associé à des exacerbations aiguës sévères de l'hépatite. Les patients infectés par le VHB qui interrompent le traitement par éfavirenz, lamivudine et fumarate de ténofovir disoproxil comprimés devraient être suivis de près avec un suivi clinique et de laboratoire pendant au moins plusieurs mois après l'arrêt du traitement. Si nécessaire, une reprise du traitement contre l'hépatite B pourra s'imposer.

Différences importantes parmi les produits contenant de la Lamivudine : Lamivudine comprimés contient une dose plus élevée du même ingrédient actif (lamivudine) que EPIVIR-VHB comprimés. EPIVIR-VHB a été développé pour les patients présentant une hépatite B chronique. La formulation et la posologie de la lamivudine dans EPIVIR-VHB ne sont pas appropriées pour les patients co-infectés par le VIH-1 et le VHB. La sécurité et l'efficacité de la lamivudine n'ont pas été établies pour le traitement de l'hépatite B chronique chez les patients co-infectés par le VIH-1 et le VHB.

Si le traitement par EPIVIR-VHB or un produit contenant du fumarate de ténofovir disoproxil tel que VIREAD est prescrit pour l'hépatite B chronique d'un patient atteint d'une infection par le VIH-1 non reconnu ou non traité, l'émergence rapide d'une résistance du VIH-1 est probable de se produire due à la dose sous-thérapeutique ou l'inadéquation de la monothérapie contre le VIH-1.

...

amaigrissement facial, une augmentation mammaire et un « aspect cushingoïde » ont été signalés chez les patients recevant une thérapie antirétrovirale combinée. Le mécanisme et les conséquences à long terme de ces événements sont actuellement inconnus. Aucun lien de causalité n'a été établi.

5.17 Allongement de l'intervalle QTc

Un allongement de l'intervalle QTc a été observé avec l'utilisation d'éfavirenz *[voir Interactions médicamenteuses (7.2, 7.5) et Pharmacologie clinique (12.2)]*. Considérer des alternatives à l'éfavirenz lorsqu'il est administré en concomitance avec un médicament ayant un risque connu de Torsade de Pointes ou lorsqu'il est administré à des patients présentant un risque plus élevé de Torsade de Pointes.

6 EFFETS INDÉSIRABLES

Les effets indésirables suivants sont discutés dans d'autres rubriques de la notice :

- Acidose lactique / hépatomégalie sévère avec stéatose [*Voir Mise en Garde Encadrée, Mises en Garde et Précautions (5.1)*].
- Exacerbations de l'hépatite B *[Voir Mise en Garde Encadrée, Mises en Garde et Précautions (5.2)]*.
- Décompensation hépatique chez les patients co-infectés par le VIH-1 et l'hépatite C [*voir Mises en garde et Précautions (5.4)*].
- Pancréatite *[Voir Mises en garde et Précautions(5.5)]*.
- Nouveau début ou aggravation d'insuffisance rénale *[Voir Mises en Garde et Précautions (5.6)]*.
- Symptômes psychiatriques *[Voir Mises en garde et Précautions(5.7)]*.
- Symptômes du système nerveux *[Voir Mises en garde et Précautions(5.8)]*.
- Éruption cutanée *[Voir Mises en garde et Précautions(5.10)]*.
- Diminution de la densité minérale osseuse *[voir Mises en garde et Précautions (5.14)]*.
- Syndrome de reconstitution immunitaire *[voir Mises en Garde et Précautions (5.15)]*.
- Redistribution de la graisse *[voir Mises en garde et Précautions(5.16)]*.

6.1 Expérience des essais cliniques

Parce que les études cliniques sont menées dans des conditions très variables, les taux des effets indésirables rapportés ne peuvent pas être directement comparés aux taux des autres études cliniques et peuvent ne pas refléter les taux observés dans la pratique clinique.

Éfavirenz, Lamivudine et Fumarate de Ténofovir Disoproxil

Patients n'ayant jamais reçu de traitement