Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets 400/300/300 mg

21098381

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SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 400 mg/300 mg /300 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 400 mg of efavirenz, 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate (equivalent to 245 mg of tenofovir disoproxil).

Excipients with known effect
Each film-coated tablet contains 133.070 mg of lactose
Each film-coated tablet contains 9.701 mg of sodium.
For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet.

Yellow coloured, oblong shaped, biconvex, film coated tablets with ''T4'' debossed on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablet is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adult and pediatric patients weighing at least 35 kg.

4.2 Posology and method of administration

Posology
Therapy should be prescribed by a physician experienced in the management of HIV-1 infection.

Testing prior to initiation and during treatment with Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablets

Prior to initiation of Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablets, test patients for hepatitis B virus infection (see section 4.4).

It is recommended that serum creatinine, serum phosphorus, estimated creatinine clearance, urine glucose, and urine protein be assessed before initiating Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablets and during therapy in all patients as clinically appropriate (see section 4.4).

Monitor hepatic function prior to and during treatment with Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablets (see section 4.4).

Recommended dosage for adult and pediatric patients weighing at least 35 kg
Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablet is a three-drug fixed-dose combination product containing 400 mg of efavirenz (EFV), 300 mg of lamivudine (3TC), and 300 mg of tenofovir disoproxil fumarate (TDF). The recommended dosage of Efavirenz/ Lamivudine/ Tenofovir disoproxil fumarate tablets in HIV-1-infected adults and pediatric patients weighing at least 35 kg is one tablet taken orally once daily.

Patients with renal impairment
Because Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablet is a fixed-dose combination tablet and cannot be dose adjusted, 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 (see section 5.2).

Patients with hepatic impairment
Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablet is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh B or C) (see section 4.4). Patients with mild hepatic impairment may be treated with Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablets without any adjustment in dose (see section 5.2).

Paediatric population
Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablet is not recommended for use in patients weighing less than 35 kg since appropriate dose adjustments cannot be made with this combination tablet.

Method of administration
Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablet is administered orally and should be taken with water and swallowed whole.

The tablet should be taken on an empty stomach, preferably at bedtime. Dosing at bedtime may improve the tolerability of nervous system symptoms (see sections 4.4 and 4.8).

4.3 Contraindications

Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablet is contraindicated:
- in patients with a previous hypersensitivity reaction (e.g., Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to the active substance or to any of the excipients listed in section 6.1 (also see section 4.4).
- when coadministered with elbasvir and grazoprevir (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Severe acute exacerbation of hepatitis B in patients coinfected with HIV-1 and HBV
Posttreatment exacerbations of hepatitis
All patients with HIV-1 should be tested for the presence of chronic hepatitis B virus (HBV) before initiating antiretroviral therapy (see section 4.2). Discontinuation of anti-HBV therapy, including 3TC and TDF, may be associated with severe acute exacerbations of hepatitis B. Patients infected with HBV who discontinue Efavirenz/Lamivudine/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
Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablets contain a higher dose of the same active ingredient, 3TC, than EPIVIR-HBV® tablets. EPIVIR-HBV was developed for patients with chronic hepatitis B. The formulation and dosage of 3TC in EPIVIR-HBV are not appropriate for patients co-infected with HIV-1 and HBV. Safety and efficacy of 3TC have not been established for treatment of chronic hepatitis B in patients co-infected with HIV-1 and HBV.

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

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

Risk of adverse reactions or loss of virologic response due to drug interactions
The concomitant use of Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablets and other drugs may result in known or potentially significant drug interactions, some of which may lead to (see sections 4.3 and 4.5):
- Loss of therapeutic effect of efavirenz, lamivudine and tenofovir disoproxil fumarate and possible development of resistance.
- Possible clinically significant adverse reactions from greater exposures of concomitant drugs.

See Table 1 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during therapy with Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablets; review concomitant medications during therapy with Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablets; and monitor for the adverse reactions associated with the concomitant drugs.

New onset or worsening renal impairment
TDF, a component of Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablet is principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of TDF (see section 4.8).

Prior to initiation and during use of Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablets, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients.

Avoid Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablets with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple non-steroidal anti-inflammatory drugs [NSAIDs]) (see section 4.5). Cases of acute renal failure after initiation of high-dose or multiple NSAIDs have been reported in HIV-infected patients with risk factors for renal dysfunction who appeared stable on TDF. Some patients required hospitalization and renal replacement therapy. Alternatives to NSAIDs should be considered, if needed, in patients at risk for renal dysfunction.

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

Psychiatric symptoms
Serious psychiatric adverse experiences have been reported in patients treated with EFV, a component of Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablet. In controlled trials of 1008 patients treated with regimens containing EFV for a mean of 2.1 years and 635 patients treated with control regimens for a mean of 1.5 years, the frequency (regardless of causality) of specific serious psychiatric events among patients who received EFV or control regimens, respectively, were severe depression (2.4%, 0.9%), suicidal ideation (0.7%, 0.3%), nonfatal suicide attempts (0.5%, 0), aggressive behavior (0.4%, 0.5%), paranoid reactions (0.4%, 0.3%), and manic reactions (0.2%, 0.3%). When psychiatric symptoms similar to those noted above were combined and evaluated as a group in a multifactorial analysis of data from a study using EFV 600 mg, treatment with EFV was associated with an increase in the occurrence of these selected psychiatric symptoms. Other factors associated with an increase in the occurrence of these psychiatric symptoms were history of injection drug use, psychiatric history, and receipt of psychiatric medication at study entry; similar associations were observed in both the EFV and control treatment groups. In a study using EFV 600 mg, onset of new serious psychiatric symptoms occurred throughout the study for both EFV-treated and control-treated patients. One percent of EFV-treated patients discontinued or interrupted treatment because of one or more of these selected psychiatric symptoms.

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

There have also been occasional post marketing reports of death by suicide, delusions, psychosis-like behavior, although a causal relationship to the use of EFV cannot be determined from these reports (see section 4.8). Post marketing cases of catatonia have also been reported and may be associated with increased efavirenz exposure. Patients with serious psychiatric adverse experiences should seek immediate medical evaluation to assess the possibility that the symptoms may be related to the use of EFV, and if so, to determine whether the risks of continued therapy outweigh the benefits.

Nervous system symptoms
Fifty-three percent (531/1008) of patients receiving EFV, a component of Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablet, in controlled trials reported central nervous system symptoms (any grade, regardless of causality) compared to 25% (156/635) of patients receiving control regimens. These symptoms included, but were not limited to, dizziness (28.1% of the 1008 patients), insomnia (16.3%), impaired concentration (8.3%), somnolence (7.0%), abnormal dreams (6.2%), and hallucinations (1.2%). These symptoms were severe in 2.0% of patients and 2.1% of patients discontinued therapy as a result. These symptoms usually begin during the first or second day of therapy and generally resolve after the first 2 to 4 weeks of therapy. After 4 weeks of therapy, the prevalence of nervous system symptoms of at least moderate severity ranged from 5% to 9% in patients treated with regimens containing EFV and from 3% to 5% in patients treated with a control regimen. Inform patients that these common symptoms were likely to improve with continued therapy and were not predictive of subsequent onset of the less frequent psychiatric symptoms (see section 4.4). Dosing at bedtime may improve the tolerability of these nervous system symptoms (see section 4.2).

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

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

Embryo-fetal toxicity
EFV, a component of Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablet, may cause fetal harm when administered during the first trimester to a pregnant woman. Advise females of reproductive potential who are receiving EFV to avoid pregnancy (see section 4.6).

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

EFV can generally be reinitiated in patients interrupting therapy because of rash. EFV should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement, or fever. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash. For patients who have had a life-threatening cutaneous reaction (e.g., Stevens-Johnson syndrome), alternate therapy should be considered (see section 4.3).

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

Hepatotoxicity
Postmarketing cases of hepatitis, including fulminant hepatitis progressing to liver failure requiring transplantation or resulting in death, have been reported in patients treated with EFV. Reports have included patients with underlying hepatic disease, including coinfection with hepatitis B or C, and patients without pre-existing hepatic disease or other identifiable risk factors.

EFV, a component of Efavirenz/ Lamivudine/ Tenofovir disoproxil fumarate tablet, is not recommended for patients with moderate or severe hepatic impairment. Careful monitoring is recommended for patients with mild hepatic impairment receiving EFV (see section 4.8).

Monitoring of liver enzymes before and during treatment is recommended for all patients (see section 4.2). Consider discontinuing Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablets in patients with persistent elevations of serum transaminases to greater than five times the upper limit of the normal range.

Discontinue Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablets if elevation of serum transaminases is accompanied by clinical signs or symptoms of hepatitis or hepatic decompensation.

Pancreatitis
In pediatric patients with a history of prior antiretroviral nucleoside exposure, a history of pancreatitis, or other significant risk factors for the development of pancreatitis, 3TC, a component of Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablet, should be used with caution. Treatment with Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablets should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur (see section 4.8).

Convulsions
Convulsions have been observed in patients receiving EFV, generally in the presence of known medical history of seizures (see section 5.3). 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 section 4.5).

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

Bone loss and mineralization effects
Bone mineral density (BMD)
In clinical trials in HIV-1-infected adults, TDF was associated with slightly greater decreases in BMD and increases in biochemical markers of bone metabolism, suggesting increased bone turnover relative to comparators (see section 4.8). Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in subjects receiving TDF.

The effects of TDF-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk in adults and pediatric subjects 2 years and older are unknown. The long-term effect of lower spine and total body BMD on skeletal growth in pediatric patients, and in particular, the effects of long-duration exposure in younger children is unknown.

Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial. Assessment of BMD should be considered for adult and pediatric patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. If bone abnormalities are suspected, then appropriate consultation should be obtained.

Mineralization defects
Cases of osteomalacia associated with proximal renal tubulopathy, manifested as bone pain or pain in extremities and which may contribute to fractures, have been reported in association with TDF use (see section 4.8). Arthralgia and muscle pain or weakness have also been reported in cases of proximal renal tubulopathy. Hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving TDF-containing products.

Immune reconstitution syndrome
Immune reconstitution syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy, including EFV, 3TC, and TDF. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

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

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.

QTc prolongation
QTc prolongation has been observed with the use of EFV (see sections 4.5 and 5.1). Consider alternatives to products containing EFV when coadministered with a drug with a known risk of Torsade de Pointes or when administered to patients at higher risk of Torsade de Pointes.

Excipients
Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablet contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablet also contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Not recommended with other antiretroviral medications
Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablet is a complete regimen for the treatment of HIV-1 infection; therefore, it should not be administered with other antiretroviral medications for treatment of HIV-1 infection.

QT prolonging drugs
There is limited information available on the potential for a pharmacodynamic interaction between EFV and drugs that prolong the QTc interval. QTc prolongation has been observed with the use of EFV (see section 5.1). Consider alternatives to EFV when coadministered with a drug with a known risk of Torsade de Pointes.

Drugs affecting renal function
Tenofovir is primarily eliminated by the kidneys (see section 5.2). Coadministration of EFV/3TC/TDF with drugs that are eliminated by active tubular secretion may increase concentrations of tenofovir and/or the coadministered drug. Some examples include, but are not limited to, acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs (see section 4.4). Drugs that decrease renal function may increase concentrations of tenofovir.

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

Established and other potentially significant interactions
EFV has been shown *in vivo* to induce CYP3A and CYP2B6. Other compounds that are substrates of CYP3A or CYP2B6 may have decreased plasma concentrations when coadministered with EFV.

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

No drug interaction studies have been conducted using Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablets. However, drug interaction studies have been conducted with the individual components of Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablet (EFV, 3TC, and TDF) (see section 5.2).

Drug interactions with EFV are summarized in Table 1 [for pharmacokinetics data see section 5.2 (Tables 10 and 11)]. This table includes potentially significant interactions but is not all inclusive.

Table 1. Established and Other Potentially Significant Drug Interactions with EFV: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect	Clinical Comment
Anticoagulant: Warfarin	↑ or ↓ warfarin	Monitor INR and adjust warfarin dosage if necessary.
Anticonvulsants: Carbamazepine	↓ carbamazepine* ↓ EFV*	There are insufficient data to make a dose recommendation for EFV. Alternative anticonvulsant treatment should be used.
Phenytoin Phenobarbital	↓ anticonvulsant ↓ EFV	Monitor anticonvulsant plasma levels periodically because of potential for reduction in anticonvulsant and/or EFV plasma levels.
Antidepressants: Bupropion	↓ bupropion*	Increases in bupropion dosage should be guided by clinical response. Bupropion dose should not exceed the maximum recommended dose.
Sertraline	↓ sertraline*	Increases in sertraline dosage should be guided by clinical response.
Antifungals: Itraconazole Ketoconazole	↓ 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.
Rifampin	↓ EFV*	Increase EFV total daily dose to 800 mg once daily when coadministered with rifampin to patients weighing 50 kg or more.
Antimalarials: Artemether/lumefantrine	↓ artemether* ↓ dihydroartemisinin* ↓ lumefantrine*	Consider alternatives to artemether/lumefantrine because of the risk of QT interval prolongation (see section 4.4).
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 EFV, dosage adjustment of calcium channel blocker may be needed and should be guided by clinical response (refer to the full prescribing information for the calcium channel blocker).
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.
Elbasvir/Grazoprevir	↓ elbasvir ↓ grazoprevir	Coadministration of EFV with elbasvir/grazoprevir is contraindicated (see section 4.3) because it may lead to loss of virologic response to elbasvir/grazoprevir.
Pibrentasvir/Glecaprevir	↓ pibrentasvir ↓ glecaprevir	Coadministration of EFV is not recommended because it may lead to reduced therapeutic effect of pibrentasvir/glecaprevir.
Simeprevir	↓ simeprevir* ↔ EFV	Concomitant administration of simeprevir is not recommended.
Velpatasvir/Sofosbuvir	↓ velpatasvir	Coadministration of EFV and sofosbuvir/velpatasvir is not recommended because it may result in loss of therapeutic effect of sofosbuvir/velpatasvir.
Velpatasvir/Sofosbuvir/ Voxilaprevir	↓ velpatasvir ↓ voxilaprevir	Coadministration of EFV and sofosbuvir/velpatasvir/voxilaprevir is not recommended because it may result in loss of therapeutic effect of sofosbuvir/velpatasvir/voxilaprevir.
Ledipasvir/Sofosbuvir	↑ TDF	Monitor for adverse reactions associated with TDF.
Hepatitis B antiviral agents Adefovir dipivoxil		Concomitant administration of adefovir dipivoxil is not recommended.
Hormonal contraceptives: Oral Ethinyl estradiol/ Norgestimate	↓ active metabolites of norgestimate*	A reliable method of barrier contraception should be used in addition to hormonal contraceptives.
Implant Etonogestrel	↓ etonogestrel	A reliable method of barrier contraception should be used in addition to hormonal contraceptives. Decreased exposure of etonogestrel may be expected. There have been postmarketing reports of contraceptive failure with etonogestrel in EFV-exposed patients.
Immunosuppressants: Cyclosporine, tacrolimus, sirolimus, and others metabolized by CYP3A	↓ immunosuppressant	Dose adjustments of the immunosuppressant may be required. Close monitoring of immunosuppressant concentrations for at least 2 weeks (until stable concentrations are reached) is recommended when starting or stopping treatment with EFV.
Narcotic analgesic: Methadone	↓ methadone*	Monitor for signs of methadone withdrawal and increase methadone dose if required to alleviate withdrawal symptoms.

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

Drugs without clinically significant interactions
No dosage adjustment is recommended when Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablet is administered with the following: aluminum/magnesium hydroxide antacids, azithromycin, cetirizine, famotidine, fluconazole, and lorazepam.

Drugs inhibiting organic cation transporters
3TC, a component of Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablet, is predominantly eliminated in the urine by active organic cationic secretion. The possibility of interactions with other drugs administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system (e.g., trimethoprim) (see section 5.2). No data are available regarding interactions with other drugs that have renal clearance mechanisms similar to that of 3TC.

Sorbitol
Coadministration of single doses of 3TC and sorbitol resulted in a sorbitol dose-dependent reduction in 3TC exposures. When possible, avoid use of sorbitol-containing medicines with 3TC (see section 5.2).

4.6 Fertility, pregnancy and lactation

Pregnancy
Efavirenz: There are retrospective post marketing reports of findings consistent with neural tube defects, including meningomyelocele, all in infants of mothers exposed to EFV-containing regimens in the first trimester (see section 4.4).

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

Lamivudine: Based on prospective reports from the APR of over 11,000 exposures to 3TC during pregnancy resulting in live births (including over 4,300 exposed in the first trimester), there was no difference between 3TC and overall risk of birth defects for 3TC compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of defects in live births was 3.1% (95% CI: 2.6% to 3.6%) following first trimester exposure to 3TC-containing regimens and 2.8% (95% CI: 2.5% to 3.3%) following second/third trimester exposure to 3TC-containing regimens.

3TC 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 3TC twice daily with zidovudine, 10 women at 38 weeks' gestation using 150 mg 3TC twice daily with zidovudine, and 10 women at 38 weeks' gestation using 3TC 300 mg twice daily without other antiretrovirals. These trials were not designed or powered to provide efficacy information.

3TC concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples. In a subset of subjects, amniotic fluid specimens were collected following natural rupture of membranes and confirmed that 3TC crosses the placenta in humans. Based on limited data at delivery, median (range) amniotic fluid concentrations of 3TC were 3.9 (1.2 to 12.8)-fold greater compared with paired maternal serum concentration (n = 8).

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

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

In published data from three controlled clinical trials, a total of 327 pregnant women with chronic HBV infection were administered tenofovir disoproxil fumarate from 28 to 32 weeks gestation through 1 to 2 months postpartum and followed for up to 12 months after delivery. There were no new safety findings in pregnant women compared with the known safety profile of tenofovir disoproxil fumarate in HBV-infected adults. An increased risk of adverse pregnancy-related outcomes was not observed; 2 stillbirths were identified, and there was 1 major birth defect (talipes) and 1 occurrence of multiple congenital abnormalities (not further specified) in tenofovir disoproxil fumarate-exposed infants. Infants were followed for up to 12 months after delivery; there were no clinically relevant drug-related safety findings in infants exposed to tenofovir disoproxil fumarate during late gestation.

Breast-feeding
Efavirenz: EFV has been shown to pass into human breast milk. There is no information available on the effects of EFV on the breastfed infant, or the effects of EFV on milk production.

Lamivudine: 3TC is present in human milk. Samples of breast milk obtained from 20 mothers receiving 3TC monotherapy, 300 mg twice daily (2 times the dose in efavirenz, lamivudine and tenofovir disoproxil fumarate), had measurable concentrations of 3TC. There is no information on the effects of 3TC on the breastfed infant, or the effects of 3TC on milk production.

Tenofovir disoproxil fumarate: Based on published data, tenofovir has been shown to be present in human breast milk (see Data). It is not known if tenofovir affects milk production or has effects on the breastfed child.

Because of the potential for (1) HIV transmission (in HIV-negative infants); (2) developing viral resistance (in HIV-positive infants); and (3) adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are receiving Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablets.

Females and males of reproductive potential
Because of potential teratogenic effects, pregnancy should be avoided in women receiving Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablets (see section 4.4).

Pregnancy testing
Females of reproductive potential should undergo pregnancy testing before initiation of Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablets.

Contraception
Females of reproductive potential should use effective contraception during treatment with Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablets and for 12 weeks after discontinuing Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablets due to the long half-life of EFV. Barrier contraception should always be used in combination with other methods of contraception. Hormonal methods that contain progesterone may have decreased effectiveness (see section 4.5).

4.7 Effects on ability to drive and use machines

No studies on the effects on ability to drive and use machines have been performed. However, dizziness has been reported during treatment with efavirenz and tenofovir disoproxil. Efavirenz may also cause impaired concentration and/or somnolence. Patients should be instructed that if they experience these symptoms, they should avoid potentially hazardous tasks such as driving and operating machinery.

4.8 Undesirable effects

The following adverse events have been reported in clinical trials during treatment of HIV-1 infection with efavirenz, lamivudine and tenofovir disoproxil.

Clinical trials in treatment-naïve HIV-1 infected adult subjects
In Trial 903, 600 antiretroviral-naïve subjects received TDF (N = 299) or stavudine (d4T) (N = 301) administered in combination with 3TC and EFV for 144 weeks. The most common adverse reactions were mild to moderate gastrointestinal events and dizziness. Mild adverse reactions (Grade 1) were common with a similar incidence in both arms and included dizziness, diarrhea, and nausea. Table 2 provides the treatment-emergent adverse reactions (Grades 2-4) occurring in greater than or equal to 5% of subjects treated in any treatment group.

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

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

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

ENCORE1 study -adverse reactions
The most common adverse reactions seen in a double-blind comparative controlled study in which 630 treatment-naïve subjects received EFV 400 mg (N = 321) or EFV 600 mg (N = 309) in combination with fixed-dose emtricitabine (FTC)/TDF for 48 weeks were mild to moderate gastrointestinal events, dizziness, abnormal dreams, and rash. Selected clinical adverse reactions of moderate or severe intensity reported in ≥ 2% of treatment-naive patients receiving combination therapy including EFV 400 mg and EFV 600 mg are presented in Table 3.

Table 3. Selected Adverse Reactions[a] (Grades 2-4) Reported in ≥ 2% in Either Treatment Group in the ENCORE1 Study through Week 48

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

[a] Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.
[b] Rash events include dermatitis allergic, drug hypersensitivity, pruritus generalized, eosinophilic pustular folliculitis, rash, rash erythematous, rash generalized, rash macular, rash maculopapular, rash morbilliform, rash papular, rash pruritic, rash vesicular, and urticaria.

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

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

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

In ENCORE1 study, a summary of Grade 3 and 4 laboratory abnormalities is provided in Table 5.

Table 5. Grades 3-4 Laboratory Abnormalities in ≥ 2% in Either Treatment Group Through Week 48

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

Pancreatitis: Pancreatitis, which has been fatal in some cases, has been observed in antiretroviral nucleoside-experienced pediatric subjects receiving 3TC alone or in combination with other antiretroviral agents (see section 4.4).

Changes in bone mineral density: In HIV-1-infected adult subjects in Trial 903, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in subjects receiving TDF + 3TC + EFV (-2.2% ± 3.9) compared with subjects receiving d4T + 3TC + EFV (-1.0% ± 4.6) through 144 weeks. Changes in BMD at the hip were similar between the two treatment groups (-2.8% ± 3.5 in the TDF group vs. -2.4% ± 4.5 in the d4T group). In both groups, the majority of the reduction in BMD occurred in the first 24-48 weeks of the trial and this reduction was sustained through Week 144. Twenty-eight percent of TDF-treated subjects vs. 21% of the d4T-treated subjects lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 subjects in the TDF group and 6 subjects in the d4T group. In addition, there were significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C telopeptide, and urinary N telopeptide) and higher serum parathyroid hormone levels and 1,25 Vitamin D levels in the TDF group relative to the d4T group; however, except for bone-specific alkaline phosphatase, these changes resulted in values that remained within the normal range (see section 4.4).

Postmarketing experience
The following adverse reactions have been identified during post-approval use for each of the individual components of Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablet (EFV, 3TC, and TDF). 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 EFV, 3TC, and TDF.

Efavirenz
Body as a whole: allergic reactions, asthenia, redistribution/accumulation of body fat (see section 4.4).

Central and peripheral nervous system: abnormal coordination, ataxia, encephalopathy, cerebellar coordination and balance disturbances, convulsions, hypoesthesia, paresthesia, neuropathy, tremor, vertigo.

Endocrine: gynecomastia.

Gastrointestinal: constipation, malabsorption.

Cardiovascular: flushing, palpitations.

Liver and biliary system: hepatic enzyme increase, hepatic failure, hepatitis.

Metabolic and nutritional: hypercholesterolemia, hypertriglyceridemia.

Musculoskeletal: arthralgia, myalgia, myopathy.

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

Respiratory: dyspnea.

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

Special senses: abnormal vision, tinnitus.

Lamivudine
Body as a whole: redistribution/accumulation of body fat (see section 4.4).

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 section 4.4).

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 section 4.4).
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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the local reporting system.

4.9 Overdose

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 EFV 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 3TC. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required because a negligible amount of 3TC 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 3TC overdose event.

Tenofovir disoproxil fumarate
Limited clinical experience at doses higher than the therapeutic dose of TDF 300 mg is available.

Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of tenofovir disoproxil fumarate, a 4-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for treatment of HIV infections, combinations; ATC code: J05AR11.

Mechanism of action
Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablet is a fixed-dose combination of antiviral drugs EFV, 3TC, and TDF with antiviral activity against HIV-1.

PATIENT INFORMATION LEAFLET

Patient information leaflet: Information for the patient

Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 400 mg/300 mg/300 mg film-coated Tablets

Efavirenz, Lamivudine and Tenofovir disoproxil fumarate

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet
1. What Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablet is and what it is used for
2. What you need to know before you take Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets
3. How to take Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets
4. Possible side effects
5. How to store Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets
6. Contents of the pack and other information

1. What Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablet is and what it is used for

Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablet is a prescription medicine that is used without other antiretroviral medicines to treat Human Immunodeficiency Virus-1 (HIV-1) in people weighing at least 35 kg.

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

Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablet contains the prescription medicines efavirenz, lamivudine and tenofovir disoproxil fumarate.

2. What you need to know before you take Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets

Do not use Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets
- If you are allergic to efavirenz, lamivudine, tenofovir disoproxil fumarate, or any of the other ingredients of this medicine (listed in section 6).
- are currently taking elbasvir and grazoprevir.

Warnings and precautions
Talk to your doctor before taking Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets:
- have liver problems, including hepatitis B or C infection
- have kidney problems, including end-stage renal disease (ESRD) that requires dialysis
- have a history of mental health problems
- have a history of drug or alcohol abuse
- have a heart problem, including QT prolongation
- have bone problems, including a history of bone fractures
- have a history of seizures

Children and adolescents
Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablet is not for use in children weighing less than 35 kg.

Other medicines and Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements.

Some medicines interact with efavirenz, lamivudine and tenofovir disoproxil fumarate. Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets may affect the way other medicines work, and other medicines may affect how Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablet works. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

You can ask your healthcare provider or pharmacist for a list of medicines that interact with Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets.

Do not start taking a new medicine without telling your healthcare provider. Your healthcare provider can tell you if it is safe to take Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets with other medicines.

You should avoid taking medicines that contain sorbitol during treatment with Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets.

Pregnancy and breast feeding
If you are pregnant or breast-feeding, think you may be pregnant, are planning to have a baby or planning to breastfeed, ask your doctor for advice before starting to use Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets.

Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets may harm your unborn baby.
You should not become pregnant during treatment with Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets. Tell your healthcare provider right away if you think you may be pregnant or become pregnant during treatment with Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets.

Females who are able to become pregnant should use effective birth control during treatment with Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets and for 12 weeks after stopping treatment. A barrier form of birth control should always be used along with another type of birth control.

If you are able to become pregnant, your healthcare provider should do a pregnancy test before you start Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets.

Do not breastfeed if you take Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets.

You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby. Talk to your healthcare provider about the best way to feed your baby.

Driving and using machines
Do not drive or use any tools or machines if you are affected after using Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets.

Efavirenz and tenofovir disoproxil fumarate may cause dizziness. Efavirenz may also cause impaired concentration, and drowsiness. Lamivudine is unlikely to affect your ability to drive or use machines.

Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets contains lactose and sodium
This medicine contains lactose monohydrate. If you have been told by your doctor that you have an intolerance to some sugars (e.g. lactose), talk to your doctor before taking this medicine.

This medicine also contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Take Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets 1 time each day, preferably at bedtime. Taking Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets at bedtime might help to make some of the side effects less bothersome.

Take Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets on an empty stomach.

Stay under the care of your healthcare provider during treatment with Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets.

If you take more Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets than you should
If you take too much Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets, go to the nearest hospital emergency room right away.

If you forget to take Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets
Do not miss a dose of Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets. If you miss a dose, take the missed dose as soon as you remember. If it is almost time for your next dose of Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets, do not take the missed dose. Take the next dose at your regular time.

If you stop taking Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets
Do not run out of Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets. The virus in your blood may increase and the virus may become harder to treat. When your supply starts to run low, get more from your healthcare provider or pharmacy.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets can cause serious side effects, including:
- **Worsening of Hepatitis B virus infection.** If you have Human Immunodeficiency Virus type 1 (HIV-1) and Hepatitis B Virus (HBV) infection, your HBV may get worse (flare-up) if you stop taking Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets. A "flare-up" is when your HBV infection suddenly returns in a worse way than before. Your healthcare provider will test you for HBV infection before you start treatment with Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets.
  - It is not known if efavirenz, lamivudine and tenofovir disoproxil fumarate is safe and effective in people who have both HIV-1 and HBV infection.
  - Do not run out of Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets. Refill your prescription or talk to your healthcare provider before your Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablet is all gone.
  - **Do not stop Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets without first talking to your healthcare provider.** If you stop taking Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets, your healthcare provider will need to check your health often and do blood tests regularly for several months to check your liver.

Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets may cause serious side effects, including:
- **Build-up of an acid in your blood (lactic acidosis).** Lactic acidosis can happen in some people who take Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets. Lactic acidosis is a serious medical emergency that can lead to death. **Call your healthcare provider right away if you get any of the following symptoms that could be signs of lactic acidosis:**
  - feel very weak or tired
  - feel cold, especially in your arms and legs
  - unusual (not normal) muscle pain
  - feel dizzy or lightheaded
  - trouble breathing
  - have a fast or irregular heartbeat
  - stomach pain with nausea or vomiting
- **Severe liver problems** can happen in people who take Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets. In some cases, these severe liver problems can lead to death. Your liver may become large (hepatomegaly) and you may develop fat in your liver (steatosis). Inflammation of your liver (hepatitis) that can lead to liver failure requiring a liver transplant has been reported in some people treated with Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets. Your healthcare provider may do blood tests to check your liver before and during treatment with Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets. **Call your healthcare provider right away if you get any of the following signs or symptoms of liver problems:**
  - your skin or the white part of your eyes turns yellow (jaundice)
  - loss of appetite for several days or longer
  - dark or "tea-colored" urine
  - nausea and vomiting
  - light-colored stools (bowel movements)
  - pain, aching, or tenderness on the right side of your stomach-area
  - confusion
  - weakness
  - tiredness
  - stomach (abdomen) swelling

You may be more likely to get lactic acidosis or serious liver problems if you are female or very overweight (obese).
- **New or worse kidney problems, including kidney failure.** Your healthcare provider may do blood and urine tests to check your kidneys before and during treatment with Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets. Tell your healthcare provider if you get signs and symptoms of kidney problems, including bone pain that does not go away or worsening bone pain, pain in your arms, hands, legs or feet, broken (fractured) bones, muscle pain or weakness.
- **Serious mental health problems. Get medical help right away if you get any of the following symptoms:**
  - feel sad or hopeless
  - are not able to move or speak normally
  - feel anxious or restless
  - have thoughts of hurting yourself (suicide) or have tried to hurt yourself or others

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SAP Caode : 21098381 (Ver. 01)
Leaflet Size: 608 x 480 mm
Colour
Black
Size After folding : 38 x 38 mm
Pharmacode: 4359_mini
Reference : New word file
Country : QCIL Uganda
Date: 14-03-2023

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- do not trust other people
- are not able to tell the difference between what is true or real and what is false or unreal
- hear or see things that are not real

- **Nervous system symptoms** are common in people who take efavirenz, lamivudine and tenofovir disoproxil fumarate and can be severe. These symptoms usually begin during the first or second day of treatment with Efavirenz/ Lamivudine/Tenofovir disoproxil fumarate Tablets and usually go away after 2 to 4 weeks of treatment. Some symptoms may occur months to years after beginning Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets therapy. These symptoms may become worse if you drink alcohol, take a medicine for mental health problems, or use certain street drugs during treatment with Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets. Symptoms may include:
  - dizziness
  - trouble concentrating
  - trouble sleeping
  - drowsiness
  - unusual dreams
  - lack of coordination or balance

If you have dizziness, trouble concentrating or drowsiness, do not drive a car, use machinery, or do anything that needs you to be alert.

Some nervous system symptoms (e.g., confusion, slow thoughts and physical movement, and delusions [false beliefs] or hallucinations [seeing or hearing things that others do not see or hear]) may occur months to years after beginning Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets therapy. Promptly contact your health care provider should any of these symptoms occur.

- **Skin reactions and allergic reactions.** Skin reactions or rash can happen and can sometimes be severe. Skin rash usually goes away without any change in treatment. If you develop a rash or a rash with any of the following symptoms, call your healthcare provider right away:
  - itching
  - peeling skin
  - fever
  - mouth sores
  - swelling of your face
  - red or inflamed eyes
  - blisters or skin lesions
- **Risk of inflammation of the pancreas (pancreatitis).** Children may be at risk for developing pancreatitis during treatment with Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets if they:
  - have taken nucleoside analogue medicines in the past
  - have a history of pancreatitis
  - have other risk factors for pancreatitis

  Call your healthcare provider right away if your child develops signs and symptoms of pancreatitis including severe upper stomach-area pain, with or without nausea and vomiting. Your healthcare provider may tell you to stop giving Efavirenz/ Lamivudine/ Tenofovir disoproxil fumarate Tablets to your child if their symptoms and blood test results show that your child may have pancreatitis.
- **Seizures.** Seizures are more likely to happen if you have had seizures in the past.
- **Increases in blood fat levels** (cholesterol and triglycerides). Your healthcare provider will check your blood fat levels before and during treatment with Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets.
- **Bone problems** can happen in some people who take Efavirenz/ Lamivudine/ Tenofovir disoproxil fumarate Tablets. Bone problems include bone pain, softening or thinning (which may lead to fractures). Your healthcare provider may need to do tests to check your bones. Tell your healthcare provider if you have any bone pain, pain in your hands or feet, or muscle pain or weakness during treatment with Efavirenz/ Lamivudine/ Tenofovir disoproxil fumarate Tablets.
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider if you start having new symptoms after starting your HIV-1 medicine.
- **Changes in body fat** can happen in some people who take HIV-1 medicines. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the main part of your body (trunk). Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known.
- **Changes in the electrical activity of your heart called QT prolongation. QT prolongation can cause irregular heartbeats that can be life-threatening.** Tell your healthcare provider if you feel faint, lightheaded, dizzy, or feel your heart beating irregularly or fast during treatment with Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets.

The most common side effects of efavirenz, lamivudine and tenofovir disoproxil fumarate are rash and dizziness.

Tell your doctor or pharmacist if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets. Call your doctor for medical advice about side effects.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the local reporting system. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date stated on the bottle and carton after 'EXP'. The expiry date refers to the last day of that month.

Do not store above 30°C. Avoid excursions above 30°C.
Discard 90 days after first opening. (This is only applicable to pack size of 90)

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets contains

- The active substance is efavirenz, lamivudine and tenofovir disoproxil fumarate. Each film-coated tablet contains 400 mg of efavirenz, 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate (equivalent to 245 mg of tenofovir disoproxil).
- The other ingredients are croscarmellose sodium, hydroxy propyl cellulose, lactose, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, starch, and yellow oxide of iron. The ingredients in the film coating are lecithin, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and yellow iron oxide.

What Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablets looks like and contents of the pack

- Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablet is presented as yellow coloured, oblong shaped, biconvex film coated tablets debossed with ''T4'' on one side and plain on other side.
- The tablets are available in bottle with non-child resistant cap containing 30 and 90 tablets.

Supplier & Manufacturer

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

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

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

Pharmacodynamic effects

Cardiac electrophysiology: The effect of EFV on the QTc interval was evaluated in an open-label, positive and placebo-controlled, fixed single sequence 3-period, 3-treatment crossover QT study in 58 healthy subjects enriched for CYP2B6 polymorphisms. The mean C_{max} of EFV in subjects with CYP2B6 *6/*6 genotype following the administration of 600 mg daily dose for 14 days was 2.25-fold the mean C_{max} observed in subjects with CYP2B6 *1/*1 genotype. A positive relationship between EFV concentration and QTc prolongation was observed. Based on the concentration-QTc relationship, the mean QTc prolongation and its upper bound 90% confidence interval are 8.7 ms and 11.3 ms in subjects with CYP2B6*6/*6 genotype following the administration of 600 mg daily dose for 14 days (see section 4.4).

Antiviral activity

Efavirenz: The concentration of EFV inhibiting replication of wild-type laboratory adapted strains and clinical isolates in cell culture by 90 to 95% ($EC_{90 to 95}$) ranged from 1.7 to 25 nM in lymphoblastoid cell lines, peripheral blood mononuclear cells (PBMCs), and macrophage/monocyte cultures. EFV demonstrated antiviral activity against clade B and most non-clade B isolates (subtypes A, AE, AG, C, D, F, G, J, N), but had reduced antiviral activity against group O viruses.

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

Tenofovir disoproxil fumarate: The antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The EC_{50} (50% effective concentration) values for tenofovir were in the range of 0.04 μM to 8.5 μM. 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 TDF against HBV.

Resistance

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

Clinical isolates with reduced susceptibility in cell culture to EFV have been obtained. One or more RT substitutions at amino acid positions A98, L100, K101, K103, V106, V108, Y188, G190, P225, F227 and M230 were observed in patients failing treatment with EFV in combination with indinavir, or with 3TC plus zidovudine. The K103N substitution was the most frequently observed.

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

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

Cross-resistance

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

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

Tenofovir disoproxil fumarate: Cross-resistance among certain HIV-1 NRTIs has been observed. The K65R and K70E substitutions selected by tenofovir are also selected in some HIV-1-infected subjects treated with abacavir or didanosine. HIV-1 isolates with the K65R substitution also showed reduced susceptibility to FTC and 3TC. HIV-1 isolates from subjects (N = 20) whose HIV-1 expressed a mean of 3 zidovudine-associated RT amino acid substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N) showed a 3.1-fold decrease in the susceptibility to tenofovir. Subjects whose virus expressed an L74V substitution without zidovudine resistance-associated substitutions (N = 8) had reduced response to VIREAD. Limited data are available for patients whose virus expressed a Y115F substitution (N = 3), Q151M substitution (N = 2), or T69 insertion (N = 4), all of whom had a reduced response.

Clinical efficacy and safety

Treatment-naïve adult patients

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

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

Trial 903: Data through 144 weeks are reported for Trial 903, a double-blind, active-controlled multicenter trial comparing EFV 600 mg + 3TC 300 mg + TDF 300 mg vs. EFV 600 mg + 3TC 300 mg + stavudine (d4T) 40 mg in 600 antiretroviral-naïve subjects. Subjects had a mean age of 36 years (range 18-64); 74% were male, 64% were Caucasian, and 20% were Black. The mean baseline CD4+ cell count was 279 cells/mm³ (range 3-956) and median baseline plasma HIV-1 RNA was 77,600 copies/mL (range 417-5,130,000). Subjects were stratified by baseline HIV-1 RNA and CD4+ cell count. Forty-three percent of subjects had baseline viral loads > 100,000 copies/mL and 39% had CD4+ cell counts < 200 cells/mm³. Table 6 provides treatment outcomes through 48 and 144 weeks.

Table 6. Outcomes of Randomized Treatment at Week 48 and 144 (Study 903)

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

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

Achievement of plasma HIV-1 RNA concentrations of < 400 copies/mL at Week 144 was similar between the two treatment groups for the population stratified at baseline on the basis of HIV-1 RNA concentration (> or ≤ 100,000 copies/mL) and CD4+ cell count (< or ≥ 200 cells/mm³). Through 144 weeks of therapy, 62% and 58% of subjects in the TDF and d4T arms, respectively, achieved and maintained confirmed HIV-1 RNA < 50 copies/mL. The mean increase from baseline in CD4+ cell count was 263 cells/mm³ for the TDF arm and 283 cells/mm³ for the d4T arm.

Through 144 weeks, 11 subjects in the TDF group and 9 subjects in the d4T group experienced a new CDC Class C event.

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

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

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

Treatment outcomes through Week 48 are presented in Table 7.

Table 7. Virologic Outcomes of Randomized Treatment in Trial ENCORE1 in Treatment-Naïve Subjects at Week 48

	At Week 48	
Outcomes (< 50 copies/mL)	EFV 400 mg + FTC + TDF (N = 321)	EFV 600 mg + FTC + TDF (N = 309)
Responder[a] HIV-1 RNA < 50 copies/mL	**86%**	**84%**
Virologic failure[b] HIV-1 RNA ≥ 50 copies/mL	11%	11%
Rebound	9%	8%
Never suppressed	2%	3%
Death	1%	1%
Discontinued for other reasons[c]	2%	4%

[a] Subjects achieved confirmed HIV-1 RNA < 50 copies/mL at Week 48.
[b] Includes confirmed viral rebound and failure to achieve confirmed < 50 copies/mL through Week 48.
[c] Includes discontinued due to Adverse Event, lost to follow-up, subject's withdrawal, noncompliance, protocol violation and other reasons.

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

5.2 Pharmacokinetic properties

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

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

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

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

Special populations

Race

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

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

Gender

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

Geriatric patients

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

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 3TC in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Patients with renal impairment

See section 4.2.

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

Lamivudine: The pharmacokinetics of 3TC are altered in subjects with renal impairment (Table 8).

Table 8. Pharmacokinetic Parameters (Mean ± SD) after a Single 300-mg Oral Dose of 3TC in Subjects with Varying Degrees of Renal Function

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

Tenofovir disoproxil fumarate: The pharmacokinetics of TDF are altered in subjects with renal impairment (see section 4.4). In subjects with creatinine clearance below 50 mL/min or with end-stage renal disease (ESRD) requiring dialysis, C_{max}, and $AUC_{0-\infty}$ of tenofovir were increased.

Table 9. Pharmacokinetic Parameters (Mean ± SD) of Tenofovir After a Single 300-mg Oral Dose of TDF in Subjects with Varying Degrees of Renal Function

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

Patients with hepatic impairment

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

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

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

Assessment of drug interactions

See section 4.5.

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

Drug interaction studies were performed with EFV and other drugs likely to be coadministered or drugs commonly used as probes for pharmacokinetic interaction. The effects of coadministration of EFV on the C_{max}, AUC, and C_{min} are summarized in Table 10 (effect of EFV on other drugs) and Table 11 (effect of other drugs on EFV). For information regarding clinical recommendations see section 4.5.

Table 10. Effect of Efavirenz on Coadministered Drug Plasma C_{max}, AUC, and C_{min}

				Coadministered Drug (mean % change)		
Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	C_{max} (90% CI)	AUC (90% CI)	C_{min} (90% CI)
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%)
Ledipasvir/ Sofosbuvir[d]	90/400 mg qd x 14 days	600 mg qd x 14 days	15	↓ 34 (↓ 25-↓ 41)	↓ 34 (↓ 25-↓ 41)	↓ 34 (↓ 24-↓ 43)
Ledipasvir				↔	↔	NA
Sofosbuvir GS-331007[e]				↔	↔	↔
Sofosbuvir[f]	400 mg qd single dose	600 mg qd x 14 days	16	↓ 19 (↓ 40-↑ 10)	↔	NA
GS-331007[e]				↓ 23 (↓ 16-↓ 30)	↓ 16 (↓ 24-↓ 8)	NA
Sofosbuvir/ Velpatasvir[g]	400/100 mg qd x 14 days	600 mg qd x 14 days	14			
Sofosbuvir				↑ 38 (↑ 14-↑ 67)	↔	NA
GS-331007[e]				↓ 14 (↓ 20-↓ 7)	↔	↔
Velpatasvir				↓ 47 (↓ 57-↓ 36)	↓ 53 (↓ 61-↓ 43)	↓ 57 (↓ 64-↓ 48)
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%)
Hydroxyitraconazole				↓ 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.
[d] Study conducted with ATRIPLA® coadministered with HARVONI®.
[e] The predominant circulating nucleoside metabolite of sofosbuvir.
[f] Study conducted with ATRIPLA coadministered with SOVALDI® (sofosbuvir).
[g] Study conducted with ATRIPLA coadministered with EPCLUSA®.
NA = not available.

Table 11. Effect of Coadministered Drug on Efavirenz Plasma C_{max}, AUC, and C_{min}

				Coadministered Drug (mean % change)		
Coadministered Drug	Dose	Efavirenz Dose	Number of Subjects	C_{max} (90% CI)	AUC (90% CI)	C_{min} (90% CI)
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: Effect of 3TC on the pharmacokinetics of other agents: Based on *in vitro* study results, 3TC at therapeutic drug exposures is not expected to affect the pharmacokinetics of drugs that are substrates of the following transporters: organic anion transporter polypeptide 1B1/3 (OATP1B1/3), breast cancer resistance protein (BCRP), P-glycoprotein (P-gp), multidrug and toxin extrusion protein 1 (MATE1), MATE2-K, organic cation transporter 1 (OCT1), OCT2, or OCT3.

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

3TC is a substrate of P-gp and BCRP; however, considering its absolute bioavailability (87%), it is unlikely that these transporters play a significant role in the absorption of 3TC. Therefore, coadministration of drugs that are inhibitors of these efflux transporters is unlikely to affect the disposition and elimination of 3TC.

Interferon alfa: There was no significant pharmacokinetic interaction between 3TC and interferon alfa in a trial of 19 healthy male subjects.

Ribavirin: *In vitro* data indicate ribavirin reduces phosphorylation of 3TC, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV-1/HCV virologic suppression) interaction was observed when ribavirin and 3TC (n = 18), stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug regimen to HIV-1/HCV co-infected subjects.

Sorbitol (excipient): 3TC and sorbitol solutions were coadministered to 16 healthy adult subjects in an open-label, randomized-sequence, 4-period, crossover trial. Each subject received a single 300-mg dose of 3TC oral solution alone or coadministered with a single dose of 3.2 grams, 10.2 grams, or 13.4 grams of sorbitol in solution. Coadministration of 3TC with sorbitol resulted in dose-dependent decreases of 20%, 39%, and 44% in the $AUC_{(0-24)}$, 14%, 32%, and 36% in the $AUC_{(\infty)}$, and 28%, 52%, and 55% in the C_{max} of lamivudine, respectively.

Trimethoprim/Sulfamethoxazole: 3TC and TMP/SMX were coadministered to 14 HIV-1positive subjects in a single-center, open-label, randomized, crossover trial. Each subject received treatment with a single 300-mg dose of 3TC and TMP 160 mg/SMX 800 mg once a day for 5 days with concomitant administration of 3TC 300 mg with the fifth dose in a crossover design. Coadministration of TMP/SMX with 3TC resulted in an increase of 43% ± 23% (mean ± SD) in 3TC AUC_{∞}, a decrease of 29% ± 13% in 3TC oral clearance, and a decrease of 30% ± 36% in 3TC renal clearance. The pharmacokinetic properties of TMP and SMX were not altered by coadministration with 3TC. There is no information regarding the effect on 3TC pharmacokinetics of higher doses of TMP/SMX such as those used in treating PCP.

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

Table 12 summarizes pharmacokinetic effects of coadministered drug on tenofovir pharmacokinetics. No clinically significant drug interactions have been observed between tenofovir and ribavirin.

Table 12. Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir[a] in the Presence of the Coadministered Drug

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

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

5.3 Preclinical safety data

Carcinogenesis, mutagenesis, impairment of fertility

Efavirenz: Long-term carcinogenicity studies in mice and rats were carried out with efavirenz. Mice were dosed with 0, 25, 75, 150, or 300 mg/kg/day for 2 years. Incidences of hepatocellular adenomas and carcinomas and pulmonary alveolar/bronchiolar adenomas were increased above background in females. No increases in tumor incidence above background were seen in males.

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

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

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

Lamivudine: Long-term carcinogenicity studies with 3TC in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) the human exposures at the recommended dose of 300 mg. 3TC was not mutagenic in a microbial mutagenicity assay, in an *in vitro* cell transformation assay, in a rat micronucleus test, in a rat bone marrow cytogenetic assay, and in assay for unscheduled DNA synthesis in rat liver. 3TC showed no evidence of *in vivo* genotoxic activity in the rat at oral doses of up to 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, 3TC administered to rats at doses up to 4000 mg per kg per day, producing plasma levels 47 to 70 times those in humans, revealed no evidence of impaired fertility and no effect on the survival, growth, and development to weaning of the offspring.

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

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

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

Pregnancy

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

Lamivudine: 3TC was administered orally to pregnant rats (at 90, 600, and 4,000 mg per kg per day) and rabbits (at 90, 300, and 1,000 mg per kg per day and at 15, 40, and 90 mg per kg per day) during organogenesis (on gestation Days 7 through 16 [rat] and 8 through 20 [rabbit]). No evidence of fetal malformations due to 3TC was observed in rats and rabbits at doses producing plasma concentrations (C_{max}) approximately 35 times higher than human exposure at the recommended daily dose. Evidence of early embryolethality was seen in the rabbit at system exposures (AUC) similar to those observed in humans, but there was no indication of this effect in the rat at plasma concentrations (C_{max}) 35 times higher than human exposure at the recommended daily dose. Studies in pregnant rats showed that 3TC is transferred to the fetus through the placenta. In the fertility/pre-and postnatal development study in rats, 3TC was administered orally at doses of 180, 900, and 4,000 mg per kg per day (from prior to mating through postnatal Day 20). In the study, development of the offspring, including fertility and reproductive performance, was not affected by maternal administration of 3TC.

Tenofovir disoproxil fumarate: TDF was administered orally to pregnant rats (at 0, 50, 150, or 450 mg/kg/day) and rabbits (at 0, 30, 100, or 300 mg/kg/day) through organogenesis (on gestation days 7 through 17, and 6 through 18, respectively). No significant toxicological effects were observed in embryo-fetal toxicity studies performed with TDF in rats at doses up to 14 times the human dose based on body surface area comparisons and in rabbits at doses up to 19 times the human dose based on body surface area comparisons. In a pre/postnatal development study in rats, TDF was administered orally through lactation at doses up to 600 mg/kg/day; no adverse effects were observed in the offspring at tenofovir exposures of approximately 2.7 times higher than human exposures at the recommended daily dose of TDF.

Animal toxicology and/or pharmacology

Efavirenz: Nonsustained convulsions were observed in 6 of 20 monkeys receiving EFV at doses yielding plasma AUC values 4-to 13-fold greater than those in humans given the recommended dose (see section 4.4).

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Croscarmellose sodium,
Hydroxy propyl cellulose,
Lactose,
Magnesium stearate,
Microcrystalline cellulose,
Sodium lauryl sulfate,
Starch
Yellow oxide of iron.

Film-coat
Lecithin
Polyethylene glycol
Polyvinyl alcohol
Talc
Titanium dioxide
Yellow iron oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30°C. Avoid excursions above 30°C.
Discard 90 days after first opening. (This is only applicable to pack size of 90)

6.5 Nature and contents of container

100 CC white HDPE container with 38 mm screw cap containing 1 x3 gm silica gel bag.
Pack size: 30 Tablets

250 CC white HDPE container with 53 mm screw cap containing 3 x 3 gm silica gel bags.
Pack size: 90 Tablets

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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