1. Name of The Medicinal Product

AVONZA Film Coated Tablet

Tenofovir Disoproxil Fumarate/Lamivudine/Efavirenz 300 mg/300 mg/400 mg[1]

[1]Trade names are not prequalified by WHO. This is under local DRA responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

2. Pharmaceutical Dosage Form

Film coated tablet

A white to off-white, film coated, oval, biconvex, beveled edge tablet debossed with M on one side of the tablet and TLE on the other side.

3. Composition

Each film-coated tablet contains:

Tenofovir Disoproxil Fumarate	300 mg
Lamivudine USP	300 mg
Efavirenz USP	400 mg

For excipients, see section 15

4. Pharmacological Properties

4.1 Pharmacodynamic Properties

- **Pharmacotherapeutic group**: Antivirals for treatment of HIV infections, combinations
- **ATC code**: J05AR11
- **Pharmacological classification**: 7.13 Antivirals
- **Mechanism of Action** : Tenofovir Disoproxil Fumarate/Lamivudine/Efavirenz Film Coated Tablets 300 mg/300 mg/400 mg are a fixed dose combination of Antiviral drugs Tenofovir Disoproxil Fumarate, Lamivudine and Efavirenz

4.2 Pharmacokinetic Properties

Tenofovir Disoproxil Fumarate/Lamivudine/Efavirenz Film Coated Tablets 300 mg/300 mg/400 mg are bioequivalent to Viread® tablets (Tenofovir Disoproxil Fumarate Tablet), Epivir® Tablet (Lamivudine 300 mg tablet) plus two tablets of Efamat® (Efavirenz 200 mg tablet) when single doses were administered to healthy volunteers under fasting conditions. Tenofovir Disoproxil Fumarate/Lamivudine/Efavirenz Film Coated Tablets 300 mg/300 mg/400 mg has not been evaluated under fed conditions. Efavirenz and other products containing Efavirenz should be administered under fasted conditions.

a. Tenofovir Disoproxil Fumarate

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

b. Lamivudine

After oral administration of 2 mg/kg of Lamivudine twice a day to 9 adults with HIV-1, the peak serum concentration (Cmax) was 1.5 ± 0.5 mcg/mL (mean ± SD). The area under the plasma concentration versus time curve (AUC) and Cmax increased in proportion to oral dose over the range from 0.25 to 10 mg/kg and absolute bioavailability in 12 adult patients was 86% ± 16% (mean ± SD) for the 150 mg tablet and 87% ± 13% for the oral solution. Binding of lamivudine to human plasma proteins is low. (less than 36%). Within 12 hours after a single oral dose of lamivudine in 6 HIV-1-infected adults, 5.2% ± 1.4% (mean ± SD) of the dose was excreted as the trans-sulfoxide metabolite in the urine 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.

c. 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. Efavirenz is highly bound (approximately 99.5 to 99,75 %) to human plasma proteins, predominantly albumin. Following administration of 14 C- labeled efavirenz, I 4 to 34% of the dose was recovered in the urine (mostly as metabolites) and 16 to 61% was recovered in feces (mostly as parent drug). In vitro studies suggest CYP3A and CYP2B6 are the major isozymes responsible for efavirenz metabolism. Efavirenz has been shown to induce CYP enzymes, resulting in induction of its own metabolism. Efavirenz has a terminal half-life of 52 to 76 hours after single doses and 40 to 55 hours after multiple doses.

5 Nonclinical Toxicology

Preclinical Safety

Carcinogenesis, Mutagenesis, Impairment of Fertility

Tenofovir Disoproxil Fumarate: Long term oral carcinogenicity studies of tenofovir disoproxil fumarate in mice and rats were carried out at exposures up to approximately 16 times (mice) and 5 times (rats) those observed in humans at the therapeutic dose for HIV-1 infections. 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 exposure up to 5 times that observed in humans at the therapeutic dose.

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

There were no effects on fertility, mating performance or early embryonic development when tenofovir disoproxil fumarate was administered to male rats at dose equivalent to 10 times the human dose based on body survace 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.

Lamivudine: Lamivudine was not mutagenic in bacterial tests but, like many nucleoside analogues, showed activity in an in vitro cytogenetic assay and the mouse lyphoma assay. Lamivudine was not genotoxic in vivo at doses that gave plasma concentrations around 40 to 50 times higher than the anticipated clinical plasma levels. As the in vitro mutagenicactivity of lamivudine could not be confirmed in in vitro tests, it is concluded that lamivudine should not represent a genotoxic hazard to patients undergoing treatment. The result of long term oral carcinogenicity studies with lamivudine in rats and mice did not show any carcinogenic potential.

Efavirenz: Efavirenz as not mutaenic or clastogenic in conventional genotoxicity assay. Efavirenz induced foetal resorptions in rats. Malformations were observed in 3 of 20 foetuses/ newborns from efavirenz treated cynomolgus monkeys given doses resulting in plasma efavirenz concentrations similar to those seen in humans. Anencephaly and unilateral anopthalmia was observed in another foetu, and cleft palate was observed in a third foetus. No malformations were observed in fetuses from efavirenz-treated rats and rabbits.

Biliary hyperplasia was observed in cynomolgus monkeys given efavirenz for ≥ 1 year at dose resultding in mean AUC values approximately 2 fold greater than those in humans given the recommended dose. The biliary hyperplasia regressed upon cessation of dosing. Biliary fibrosis has been observed in rats. Non-sustained convulsions were observed in some monkeys receiving efavirenz for ≥ year, at doses yielding plasma AUC values 4-to-13-fold greater than those in humans given the recommended dose.

Animal Toxicology

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

Evidence of renal toxicity was noted in 4 animal species. Increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate were

observed to varying degrees in these animals. The toxicities were noted at exposures (based on AUCs) 2-20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia, to the bone toxicity is not known.

Lamivudine: Reproductive studies in animals have not shown evidence of teratogenicity, and showed no effect on male or female fertility. Lamivudine produced small increases in early embryonic loss when administered to pregnant rabbits, at exposure levels comparable to those achieved in man. However, there as in evidence of embryonic loss in rats at exposure levels of approximately 35 times the clinical exposure (based on Cmax).

Administration of Lamivudine in animal toxicity studies at very high doses was not associated with any major organ toxicity. Reductions of erythrocyte and neutrophil counts were identified as the effects most likely to be relevance.

Efavirenz: Studies in animals have shown reproductive toxicity including marked teratogenic effects. Therefore, efavirenz should not be used during pregnancy unless clearly necessary (the potential benefit to the mother outweighs the potential risks to the foetus and there are no other appropriate treatment options). Pregnancy should be avoided in women receiving Efavirenz.

6 Therapeutic Indication

Tenofovir Disoproxil Fumarate/Lamivudine/Efavirenz 300 mg/300 mg/400 mg film coated tablet is indicated for the treatment of HIV infection in adults.

7 Posology and Method of Administration

The recommended dose of Tenofovir Disoproxil Fumarate/Lamivudine/Efavirenz 300 mg/300 mg/400 mg film coated tablet is one tablet taken orally once daily on an empty stomach, preferably at bedtime. This combination is not recommended for use in pediatric (less than 18 years).

8 Contraindications

8.1 Hypersensitivity

Tenofovir disoproxil fumarate/Lamivudine/Efavirenz is contraindicated in patients with previously demonstrated, clinically significant hypersensitivity (eg, Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the components contained in the formulation.

8.2 Contraindicated Drugs

For some drugs, competition for CYP3A by Efavirenz, a component of Tenofovir disoproxil fumarate/Lamivudine/Efavirenz, could result in inhibition of their metabolism and create the potential for serious and/or life-threatening adverse reactions (eg, cardiac arrhythmias, prolonged sedation, or respiratory depression). Drugs that are contraindicated with Tenofovir disoproxil fumarate/Lamivudine/Efavirenz Tablets are listed in Table 1.

Table 1: Drugs That Are Contraindicated or Not Recommended for Use With	
Drug Class: Drug Name /Patient's Condition	**Clinical Comment**
Antimigraine:ergot 0derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine)	Potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
Astemizole	Potential for serious and/or life-threatening reactions
Benzodiazepines: midazolam, triazolam	Potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.
Calcium channel blocker: bepridil	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
GI motility agent: cisapride	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Neuroleptic: pimozide	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
St. John's wort *(Hypericum perforatum)*	May lead to loss of virologic response and possible resistance to efavirenz or to the class of non- nucleoside reverse transcriptase inhibitors (NNRTIs).
Terfenadine	Potential for serious and/or life-threatening reactions
Patients with previously demonstrated clinically significant hypersensitivity (e.g., anaphylaxis) to any of the components of the products.	-

Efavirenz is contraindicated in patients with severe hepatic impairment (Child Pugh Class C)

9 Special Warnings and Precautions for Use

9.1 **Lactic Acidosis/Severe Hepatomegaly With Steatosis**

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

9.2 **Patients Coinfected with HIV-1 and HBV**

It is recommended that all patients with HIV-1 be tested for the presence of chronic hepatitis B virus (HBV) before initiating antiretroviral therapy. Discontinuation of anti-HBV therapy, including lamivudine and tenofovir disoproxil fumarate, may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue Tenofovir Disoproxil Fumarate, Lamivudine and Efavirenz 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.

Emergence of Lamivudine-Resistant HBV: In non-HIV-1-infected patients treated with lamivudine for chronic hepatitis B, emergence of lamivudine-resistant HBV has been detected and has been associated with diminished treatment response (see full prescribing information for EPIVIR-HBV for additional information). Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been reported in HIV-1-infected patients who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus.

9.3 **Coadministration with Other Products**

Tenofovir disoproxil fumarate/Lamivudine/Efavirenz is a fixed dose combination product and should not be coadministered concomitantly with other Tenofovir-containing, Lamivudine-containing, Efavirenz-containing or Emtricitabine-containing drugs. Tenofovir disoproxil fumarate, Lamivudine, and Efavirenz should not be administered in combination with Adefovir Disoproxil.

9.4 **Use With Interferon- and Ribavirin-Based Regimens**

In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine, a component of Tenofovir disoproxil fumarate, Lamivudine and Efavirenz. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV-1/HCV co-infected patients *[see Clinical Pharmacology (12.3)]*, hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin. Patients receiving interferon alfa with or without ribavirin and lamivudine should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of lamivudine

should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Child-Pugh >6). See the complete prescribing information for interferon and ribavirin.

9.5 **Pancreatitis**

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

9.6 **New Onset or Worsening Renal Impairment**

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

It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with tenofovir disoproxil fumarate. Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment, including patients who have previously experienced renal events while receiving adefovir dipivoxil. Tenofovir disoproxil fumarate, Lamivudine and Efavirenz should be avoided with concurrent or recent use of a nephrotoxic agent.

9.7 **Psychiatric Symptoms**

Serious psychiatric adverse experiences have been reported in patients treated with efavirenz. Patients with a history of psychiatric disorders appear to be at greater risk of these serious psychiatric adverse experiences. There have also been occasional postmarketing reports of death by suicide, delusions, and psychosis-like behavior, although a causal relationship to the use of efavirenz cannot be determined from these reports. Patients should be advised that if they experience these symptoms they should contact their doctor immediately to assess the possibility that the symptoms may be related to use of efavirenz, and if so, to determine whether the risks of continued therapy outweigh the benefits.

9.8 **Nervous System Symptoms**

Fifty-three percent (531/1008) of patients receiving efavirenz, a component of Tenofovir disoproxil fumarate, Lamivudine and Efavirenz, in controlled trials reported central nervous system symptoms (any grade, regardless of causality) compared to 25% (156/635) of patients receiving control regimens. These symptoms included, but were not limited to, dizziness (28.1% of the 1008 patients), insomnia (16.3%), impaired concentration (8.3%), somnolence (7.0%), abnormal dreams (6.2%), and hallucinations (1.2%). These symptoms were severe in 2.0% of patients and 2.1% of patients discontinued therapy as a result. These symptoms usually begin during the first or second day of therapy and generally resolve after the first 2 to 4 weeks of therapy. After 4 weeks of therapy, the prevalence of nervous system symptoms of at least moderate severity ranged from 5% to 9% in patients treated with regimens containing efavirenz and

from 3% to 5% in patients treated with a control regimen. Patients should be informed that these common symptoms were likely to improve with continued therapy and were not predictive of subsequent onset of the less frequent psychiatric symptoms [see *Warnings and Precautions*]. Dosing at bedtime may improve the tolerability of these nervous system symptoms [see *Dosage and Administration]*.

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

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

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

9.9 **Reproductive Risk Potential**

Pregnancy Category D. Efavirenz, a component of Tenofovir disoproxil fumarate, Lamivudine and Efavirenz, may cause fetal harm when administered during the first trimester to a pregnant woman. Pregnancy should be avoided in women receiving efavirenz. Barrier contraception must always be used in combination with other methods of contraception (eg, oral or other hormonal contraceptives). Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of efavirenz is recommended. Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz. If this drug is used during the first trimester of pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus.

There are no adequate and well-controlled studies in pregnant women. Efavirenz should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus, such as in pregnant women without other therapeutic options. [See *Use in Specific Populations*]

9.10 **Rash**

Mild-to-moderate rash has been reported in clinical trials with efavirenz and usually resolves with continued therapy. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash. Severe rash associated with blistering, moist desquamation or ulceration has been reported in less than 1% of patients treated with efavirenz. The incidence of erythema multiforme or Stevens-Johnson Syndrome was 0.14% efavirenz should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement of fever. If therapy with efavirenz is discontinued, consideration should also be given to interrupting therapy with other anti-retroviral agents to avoid development of drug resistant virus. Patients who discontinued treatment with other NNRTIs due to rash may be at higher risk of developing rash during treatment with efavirenz.

9.11 **Hepatotoxicity**

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

9.12 **Convulsions**

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

9.13 **Lipid Elevations**

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

9.14 **Decreases in Bone Mineral Density**

Assessment of bone mineral density (BMD) should be considered for adults and pediatric patients 12 years of age and older who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained.

In HIV-1 infected adult subjects treated with tenofovir disoproxil fumarate, a component of Tenofovir disoproxil fumarate/Lamivudine/Efavirenz, in published paper study 903 through 144 weeks, decreases from baseline in BMD were seen at the lumbar spine and hip in both arms of the study. At Week 144, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in subjects receiving tenofovir disoproxil fumarate + lamivudine + efavirenz (-2.2% ± 3.9) compared with subjects receiving stavudine + lamivudine + efavirenz (-1.0% ± 4.6). Changes in BMD at the hip were similar between the two treatment groups (-2.8% ± 3.5 in the tenofovir disoproxil fumarate group vs. -2.4% ± 4.5 in the stavudine group). In both groups, the majority of the reduction in BMD occurred in the first 24 to 48 weeks of the study and this reduction was sustained through Week 144. Twenty-eight percent of tenofovir disoproxil fumarate-treated subjects vs. 21% of the stavudine-treated subjects lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 subjects in the tenofovir disoproxil fumarate group and 6 subjects in the stavudine group. In addition, there were significant

increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide, and urinary N-telopeptide) in the tenofovir disoproxil fumarate group relative to the stavudine group, suggesting increased bone turnover. Serum parathyroid hormone levels and 1, 25 Vitamin D levels were also higher in the tenofovir disoproxil fumarate group. Except for bone specific alkaline phosphatase, these changes resulted in values that remained within the normal range. The effects of tenofovir disoproxil fumarate-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. Cases of osteomalacia (associated with proximal renal tubulopathy and which may contribute to fractures) have been reported in association with the use of tenofovir disoproxil fumarate *[See Adverse Reactions]*. The bone effects of tenofovir disoproxil fumarate have not been studied in patients with chronic HBV infection.

9.15 **Immune Reconstitution Syndrome**

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

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

9.16 **Fat Redistribution**

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

10 Drug Interaction

No drug interaction studies have been conducted using Tenofovir disoproxil fumarate, Lamivudine and Efavirenz. However, drug interaction studies have been conducted with the individual components Tenofovir disoproxil fumarate, Lamivudine and Efavirenz *[see Clinical Pharmacology]*.

Efavirenz

10.1. Drug-Drug Interactions

Efavirenz has been shown *in vivo* to induce CYP3A and CYP2B6. Other compounds that are substrates of CYP3A or CYP2B6 may have decreased plasma concentrations when coadministered with efavirenz. *In vitro* studies have demonstrated that efavirenz inhibits CYP2C9, 2C19, and 3A4 isozymes in the range of observed efavirenz plasma concentrations. Coadministration of efavirenz with drugs primarily metabolized by these isozymes may result in altered plasma concentrations of the coadministered drug. Therefore, appropriate dose adjustments may be necessary for these drugs.

Drugs that induce CYP3A activity (eg, phenobarbital, rifampin, rifabutin) would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations. Drug interactions with efavirenz are summarized in Tables 1 and 2 [for pharmacokinetics data see *Clinical Pharmacology*]. The tables include potentially significant interactions, but are not all inclusive.

Table 2: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen

May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	**Effect**	**Clinical Comment**
HIV antiviral agents		
Protease inhibitor: Fosamprenavir Calcium	↓ amprenavir	Fosamprenavir (unboosted): Appropriate doses of the combinations with respect to safety and efficacy have not been established. Fosamprenavir/ritonavir: An additional 100 mg/day (300 mg total) of ritonavir is recommended when efavirenz is administered with fosamprenavir/ritonavir once daily. No change in the ritonavir dose is required when efavirenz is administered with fosamprenavir plus ritonavir twice daily.
Protease inhibitor: Atazanavir	↓ atazanavir*	Treatment-naïve patients: When coadministered with efavirenz, the recommended dose of atazanavir is 400 mg with ritonavir 100 mg (together once daily with food) and efavirenz 600 mg (once daily on an empty stomach, preferably at bedtime). Treatment-experienced patients: Coadministration of efavirenz and atazanavir is not recommended.
Protease inhibitor: Indinavir	↓ indinavir*	The optimal dose of indinavir, when given in combination with efavirenz, is not known. Increasing the indinavir dose to 1000 mg every 8 hours does not compensate for the increased indinavir metabolism due to efavirenz. When indinavir at an increased dose (1000 mg every 8 hours) was given with efavirenz (600 mg once daily), the indinavir AUC and Cmin were

		decreased on average by 33 to 46% and 39 to 57%, respectively, compared to when indinavir (800 mg every 8 hours) was given alone.
Protease inhibitor: Lopinavir/ritonavir	↓ lopinavir*	Lopinavir/ritonavir tablets should not be administered once daily in combination with efavirenz. In antiretroviral-naive patients, lopinavir/ritonavir tablets can be used twice daily in combination with efavirenz with no dose adjustment. A dose increase of lopinavir/ritonavir tablets to 600/150 mg (3 tablets) twice daily may be considered when used in combination with efavirenz in treatment- experienced patients where decreased susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). A dose increase of lopinavir/ritonavir oral solution to 533/133 mg (6.5 mL) twice daily taken with food is recommended when used in combination with efavirenz.
Protease inhibitor: Ritonavir	↑ ritonavir* ↑ efavirenz*	When ritonavir 500 mg q12h was coadministered with efavirenz 600 mg once daily, the combination was associated with a higher frequency of adverse clinical experiences (eg, dizziness, nausea, paresthesia) and laboratory abnormalities (elevated liver enzymes). Monitoring of liver enzymes is recommended when efavirenz is used in combination with ritonavir.
Protease inhibitor: Saquinavir	↓ saquinavir*	Should not be used as sole protease inhibitor in combination with efavirenz.
NNRTI: Other NNRTIs	↑ or ↓ efavirenz and/or NNRTI	Combining two NNRTIs has not been shown to be beneficial. Efavirenz should not be coadministered with other NNRTIs.
CCR5 co-receptor antagonist: Maraviroc	↓ maraviroc	Refer to the full prescribing information for maraviroc for guidance on Coadministration with efavirenz.
Integrase strand transfer inhibitor:	↓raltregravir	Efavirenz reduces plasma concentrations of raltegravir. The clinical significance of this interaction has not been directly assessed.

Raltegravir		
Hepatitis C antiviral agents		
Protease inhibitor: Boceprevir	↓ boceprevir	Plasma trough concentrations of boceprevir were decreased when boceprevir was coadministered with efavirenz, which may result in loss of therapeutic effect. The combination should be avoided.
Protease inhibitor: Telaprevir	↓ telaprevir* ↓ efavirenz*	Concomitant administration of telaprevir and efavirenz resulted in reduced steady-state exposures to telaprevir and efavirenz.
Other agents		
Anticoagulant: Warfarin	↑ or ↓ warfarin	Plasma concentrations and effects potentially increased or decreased by efavirenz.
Anticonvulsants: Carbamazepine	↓ carbamazepine ↓ efavirenz*	There are insufficient data to make a dose recommendation for efavirenz. Alternative anticonvulsant treatment should be used.
Phenytoin, Phenobarbital	↓ anticonvulsant ↓ efavirenz	Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.
Antidepressants : Bupropion, Sertraline	↓ bupropion* ↓ sertraline*	The effect of efavirenz on bupropion exposure is thought to be due to the induction of bupropion metabolism. Increases in bupropion dosage should be guided by clinical response, but the maximum recommended dose of bupropion should not be exceeded. Increases in sertraline dosage should be guided by clinical response.
Antifungals: Voriconazole	↓ voriconazole* ↑ efavirenz*	Efavirenz and voriconazole must not be coadministered at standard doses. Efavirenz significantly decreases voriconazole plasma concentrations, and coadministration may decrease the therapeutic effectiveness of voriconazole. Also, voriconazole significantly increases efavirenz plasma concentrations, which

		may increase the risk of efavirenz-associated side effects. When voriconazole is coadministered with efavirenz, voriconazole maintenance dose should be increased to 400 mg every 12 hours and efavirenz dose should be decreased to 300 mg once daily using the capsule formulation. Efavirenz tablets should not be broken. [See *Clinical Pharmacology (12.3, Tables 5* and 6).]
Itraconazole	↓ itraconazole* ↓ hydroxyitraconazole*	Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered.
Ketoconazole	↓ ketoconazole	Drug interaction studies with efavirenz and ketoconazole have not been conducted. Efavirenz has the potential to decrease plasma concentrations of ketoconazole.
Posaconazole	↓ posaconazole*	Avoid concomitant use unless the benefit outweighs the risks.
Anti-infective: Clarithromycin	↓ clarithromycin* ↑ 14-OH metabolite*	Plasma concentrations decreased by efavirenz; clinical significance unknown. In uninfected volunteers, 46% developed rash while receiving efavirenz and clarithromycin. No dose adjustment of efavirenz is recommended when given with clarithromycin. Alternatives to clarithromycin, such as azithromycin, should be considered (see *Other Drugs,* following table). Other macrolide antibiotics, such as erythromycin, have not been studied in combination with efavirenz.
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	↓ efavirenz*	If efavirenz is coadministered with rifampin to patients weighing 50 kg or more, an increase in the dose of efavirenz to 800 mg once daily is recommended.
Calcium Channel	↓ diltiazem* ↓ desacetyl diltiazem*	Diltiazem dose adjustments should be guided by clinical response (refer to the full prescribing information for diltiazem). No dose adjustment

Blockers: Diltiazem	↓N-monodesmethyl diltiazem*	of efavirenz is necessary when administered with diltiazem.
Others (eg.Felodipine, Nicardipine, Nifedipine, Verapamil)	↓calcium channel blocker	No data are available on the potential interactions of efavirenz with other calcium channel blockers that are substrates of CYP3A. The potential exists for reduction in plasma concentrations of the calcium channel blocker. Dose adjustments 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.
Hormonal contraceptives: Oral Ethinyl estradiol/ Norgestimate Implant Etonogestrel	↓active metabolites of norgestimate* ↓etonogestrel	A reliable method of barrier contraception must be used in addition to hormonal contraceptives. Efavirenz had no effect on ethinyl estradiol concentrations, but progestin levels (norelgestromin and levonorgestrel) were markedly decreased. No effect of ethinyl estradiol/ norgestimate on efavirenz plasma concentrations was observed. A reliable method of barrier contraception must be used in addition to hormonal contraceptives. The interaction between etonogestrel and efavirenz has not been studied. Decreased exposure of etonogestrel may be expected. There have been postmarketing reports of contraceptive failure with etonogestrel in efavirenz-exposed patients.
Immunosuppressant: Cyclosporine, tacrolimus, sirolimus, and others metabolized by CYP3A	↓ immunosuppressant	Decreased exposure of the immunosuppressant may be expected due to CYP3A induction. These immunosuppressants are not anticipated to affect exposure of efavirenz. Dose adjustments of the immunosuppressant may be required. Close monitoring of immunosuppressant concentrations for at least 2 weeks (until stable concentrations are reached) is

		recommended when starting or stopping treatment with efavirenz.
Narcotic analgesic: Methadone	↓ methadone*	Coadministration in HIV-infected individuals with a history of injection drug use resulted in decreased plasma levels of methadone and signs of opiate withdrawal. Methadone dose was increased by a mean of 22% to alleviate withdrawal symptoms. Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.

*The interaction between efavirenz and the drug was evaluated in a clinical study. All other drug interactions shown are predicted.

**This table is not all-inclusive.

Other Drugs

Based on the results of drug interaction studies [see *Clinical Pharmacology (12.3, Tables 5* and 6)], no dosage adjustment is recommended when efavirenz is given with the following: aluminum/magnesium hydroxide antacids, azithromycin, cetirizine, famotidine, fluconazole, lamivudine, lorazepam, nelfinavir, paroxetine, tenofovir disoproxil fumarate, and zidovudine.

Specific drug interaction studies have not been performed with efavirenz and NRTIs other than lamivudine and zidovudine. Clinically significant interactions would not be expected since the NRTIs are metabolized via a different route than efavirenz and would be unlikely to compete for the same metabolic enzymes and elimination pathways.

10.2. Cannabinoid Test Interaction

Efavirenz does not bind to cannabinoid receptors. False-positive urine cannabinoid test results have been observed in non-HIV-infected volunteers receiving efavirenz when the Microgenics CEDIA DAU Multi-Level THC assay was used for screening. Negative results were obtained when more specific confirmatory testing was performed with gas chromatography/mass spectrometry.

Of the three assays analyzed (Microgenics CEDIA DAU Multi-Level THC assay, Cannabinoid Enzyme Immunoassay [Diagnostic Reagents, Inc], and AxSYM Cannabinoid Assay), only the Microgenics CEDIA DAU Multi-Level THC assay showed false-positive results. The other two assays provided true-negative results. The effects of efavirenz on cannabinoid screening tests other than these three are unknown. The manufacturers of cannabinoid assays should be contacted for additional information regarding the use of their assays with patients receiving efavirenz.

Lamivudine

Lamivudine is predominantly eliminated in the urine by active organic cationic secretion. The possibility of interactions with other drugs administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system (e.g., trimethoprim).

No data are available regarding interactions with other drugs that have renal clearance mechanisms similar to that of lamivudine.

10.3. Interferon- and Ribavirin-Based Regimens

Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV-1/HCV co-infected patients, hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination.antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin *[see Warnings and Precautions, Clinical Pharmacology].*

10.4. Trimethoprim/Sulfamethoxazole (TMP/SMX)

No change in dose of either drug is recommended. There is no information regarding the effect on lamivudine pharmacokinetics of higher doses of TMP/SMX such as those used to treat PCP.

10.5. Zidovudine

A modest increase in Cmax (28%) was observed for Zidovudine when administered with Lamivudine, however overall exposure (AUC) was not significantly altered. Zidovudine had no effect on the pharmacokinetics of Lamivudine.

10.6. Zalcitabine

Lamivudine may inhibit the intracellular phosphorilation of Zalcitabine when the two medical products are use concurrently. Lamivudine is therefor not reccomended to be use in combination with Zalcitabine.

Tenofovir Disoproxil Fumarate

10.7. Didanosine

Coadministration of tenofovir disoproxil fumarate and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse reactions. Didanosine should be discontinued in patients who develop didanosine-associated adverse reactions.

When administered with tenofovir disoproxil fumarate, the C_{max} and AUC of didanosine (administered as either the buffered or enteric-coated formulation) increased significantly *[See Clinical Pharmacolog]*. The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis, and neuropathy. Suppression of CD4+ cell counts has been observed in patients receiving tenofovir disoproxil fumarate (tenofovir DF) with didanosine 400 mg daily.

In patients weighing greater than 60 kg, the didanosine dose should be reduced to 250 mg when it is coadministered with tenofovir DF. Data are not available to recommend a dose adjustment of didanosine for adults or pediatric patients weighing less than 60 kg. When coadministered, tenofovir disoproxil fumarate and didanosine enteric coated capsule may be taken under fasted conditions or with a light meal (less than 400 kcal, 20% fat). Coadministration of didanosine buffered tablet formulation with tenofovir disoproxil fumarate should be under fasted conditions.

10.8. Atazanavir

Atazanavir has been shown to increase tenofovir concentrations *[See Clinical Pharmacology]*. The mechanism of this interaction is unknown. Patients receiving atazanavir and tenofovir disoproxil fumarate should be monitored for tenofovir disoproxil fumarate-associated adverse reactions. Tenofovir Disoproxil Fumarate should be discontinued in patients who develop tenofovir disoproxil fumarate-associated adverse reactions.

Tenofovir Disoproxil Fumarate decreases the AUC and C_{min} of atazanavir *[See Clinical Pharmacology]*. When coadministered with tenofovir disoproxil fumarate, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. Atazanavir without ritonavir should not be coadministered with tenofovir disoproxil fumarate.

10.9. Lopinavir/Ritonavir

Lopinavir/Ritonavir has been shown to increase tenofovir concentrations *[See Clinical Pharmacology]*. The mechanism of this interaction is unknown. Patients receiving lopinavir/ritonavir and tenofovir disoproxil fumarate should be monitored for tenofovir disoproxil fumarate-associated adverse reactions. Tenofovir Disoproxil Fumarate should be

discontinued in patients who develop tenofovir disoproxil fumarate-associated adverse reactions.

10.10. Drugs Affecting Renal Function

Since tenofovir is primarily eliminated by the kidneys *[See Clinical Pharmacology]*, coadministration of tenofovir disoproxil fumarate with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir and/or increase the concentrations of other renally eliminated drugs. Some examples include, but are not limited to cidofovir, acyclovir, valacyclovir, ganciclovir, and valganciclovir. Drugs that decrease renal function may also increase serum concentrations of tenofovir. In the treatment of chronic hepatitis B, tenofovir disoproxil fumarate should not be administered in combination with HEPSERA (adefovir dipivoxil).

11 Special Population

Pregnancy and Lactation

Pregnancy Category D: *See Warnings and Precautions*

11.1 **Nursing Mothers**

It is recommended that HIV-1 infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. Because of both the potential for HIV-1 transmission and serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving Tenofovir disoproxil fumarate, Lamivudine and Efavirenz.

11.2 **Pediatric Use**

Tenofovir disoproxil fumarate/Lamivudine/Efavirenz Film Coated Tablets is recommended for use in pediatric (< 18 years). No data are available.

11.3 **Geriatric Use**

Clinical studies of Tenofovir disoproxil fumarate, Lamivudine and Efavirenz did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly patient should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

11.4 Patients with impaired renal function

No data are available for use Tenofovir disoproxil fumarate/Lamivudine/Efavirenz Fixed Dose Combination Tablet in patients renal impairment.

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

11.5 Hepatic Impairment

No data are available for use Tenofovir disoproxil fumarate/Lamivudine/Efavirenz Fixed Dose Combination Tablet in patients hepatic impairment.

Efavirenz, a component of Tenofovir disoproxil fumarate, Lamivudine and Efavirenz, is contraindicated for patients with severe hepatic impairment. Efavirenz is not recommended for patients with moderate hepatic impairment because there are insufficient data to determine whether dose adjustment is necessary. Patients with mild hepatic impairment may be treated with efavirenz without any adjustment in dose. Because of the extensive cytochrome P450-mediated metabolism of efavirenz and limited clinical experience in patients with hepatic impairment, caution should be exercised in administering efavirenz to these patients.

12 Effect on Ability to Drive and Use Machine

Efavirenz may cause dizziness, impaired concentration, and/or somnolence. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery.

13 Adverse Reactions (Undesirable Effect)

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

- Lactic Acidosis/Severe Hepatomegaly with Steatosis *[See Boxed Warning, Warnings and Precautions]*.
- Severe Acute Exacerbations of Hepatitis B *[See Boxed Warning, Warnings and Precautions]*.
- Hepatic decompensation in patients co-infected with HIV-1 and Hepatitis C *[See Warnings and Precautions]*.
- Pancreatitis *[See Warnings and Precautions].*
- New Onset or Worsening Renal Impairment *[See Warnings and Precautions]*.
- Psychiatric symptoms *[see Warnings and Precaution]*
- Nervous system symptoms *[see Warnings and Precaution]*.
- Rash *[see Warnings and Precautions]*.- Decreases in Bone Mineral Density *[See Warnings and Precautions]*.
- Immune Reconstitution Syndrome *[See Warnings and Precautions]*

13.1 Clinical Trials Experience

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

Tenofovir disoproxil fumarate, Lamivudine and Efavirenz

Treatment-Naïve Patients

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

Mild adverse reactions (Grade 1) were common with a similar incidence in both arms, and included dizziness, diarrhea, and nausea. Selected treatment-emergent moderate to severe adverse reactions are summarized in Table 3.

Table 3. Selected Treatment-Emergent Adverse Reactions[a] (Grades 2 to 4) Reported in [3]5% in Any Treatment Group in Study 903 (0 to 144 Weeks)

	Tenofovir disoproxil fumarate + 3TC + EFV	d4T + 3TC + EFV
	N=299	N=301
Body as a Whole		
Headache	14%	17%
Pain	13%	12%
Fever	8%	7%
Abdominal pain	7%	12%
Back pain	9%	8%
Asthenia	6%	7%
Digestive System		
Diarrhea	11%	13%
Nausea	8%	9%
Dyspepsia	4%	5%
Vomiting	5%	9%
Metabolic Disorders		
Lipodystrophy[b]	1%	8%
Musculoskeletal		
Arthralgia	5%	7%
Myalgia	3%	5%
Nervous System		
Depression	11%	10%
Insomnia	5%	8%

Dizziness	3%	6%
Peripheral neuropathy[c]	1%	5%
Anxiety	6%	6%
Respiratory		
Pneumonia	5%	5%
Skin and Appendages		
Rash event[d]	18%	12%

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

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

Table 4 Grade 3/4 Laboratory Abnormalities Reported in [3]1% of Patients Randomized to Tenofovir disoproxil fumarate, Lamivudine and Efavirenz in Study 903 (0–144 Weeks)

	TDF+ 3TC + EFV	**d4T + 3TC + EFV**
	N=299	**N=301**
Any[3] 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%

13.2 **Postmarketing Experience**

The following adverse reactions have been reported during postmarketing use for each of the individual components of Tenofovir disoproxil fumarate Lamivudine, and Efavirenz. Because these reactions are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These reactions have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to lamivudine and tenofovir DF.

Tenofovir Disoproxil Fumarate

- Immune System Disorders : Allergic reaction, including angioedema
- Metabolism and Nutrition Disorder : Lactic acidosis, hypokalemia, hypophosphatemia
- Respiratory, Thoracic, and Mediastinal Disorders : Dyspnea
- Gastrointestinal disorders : Pancreatitis, increased amylase, abdominal pain
- Hepatobiliary Disorders : Hepatic steanosis, hepatitis, increased liver enzymes (most commontly 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
- Renal and Urinary Disorders : Acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal insufficiency, increased creatinine, proteinuria, poliuria.
- General Disorders and Administration Site Conditions: Astemia
- The following adverse reaction listed under the body system heading above, may occur as a consequence of proximal renal tubulopathy: Rhabdomyolisis, Osteomalacia, Hypokalemia, Muscular Weakness, Myopathy, Hypophosphatemia.

Lamivudine

- Body as Whole : Redistribution/accumulation of body fat
- Endocrine and Metabolic : Hyperglycemia
- General : Weakness
- Hemic and Lymphatic : Anemia (including pure red cell aplasia and severe anemias progressing on therapy)
- Hepatic and Pancreatic : Lactic acidosis and hepatic steatosis, posttreatment exacerbations of hepatitis B
- Hypersensitivity : Anaphylaxis, urticaria
- Musculoskletal : Muscle weakness, CPK evaluation, rhabdomyolysis
- Skin : Alopecia, pruritus,

Efavirenz

- Body as Whole : allergic reaction, asthenia, redistribution/accumulation of body fat
- Central and Peripheral Nervous System : abnormal coordination, ataxia, cerebellar coordination and balance disturbances, convulsion, hypoesthesia, paresthesia, neuropathy, tremor, vertigo,
- Endocrine : gynecomastia
- Gastrointestinal : constipation, malabsorption
- Cardiovascular : flushing, palpitations
- Liver and Biliary System : hepatic enzyme increase, hepatic failure, hepatitis. A few of the postmarketing reports of hepatic failure, including cases in patients with no pre-existing hepatic disease or other identifiable risk factors were characterized by a fulminant course, progressing in some cases to transplantation or death
- Metabolic and Nutritional : hypercholesterolemia, hypertrigliceridemia
- Musculoskletal : arthalgia, myalgia, myopathy
- Psychiatric : aggresive reactions, agitation, delusions, emotional lability, mania, neurosis, paranoia, psycosis, suicide, catatonia
- Respiratory : dyspnea
- Skin and Appendages : erythema multiforme, photoallergic dermatitis, Stevens-Johnson syndrome
- Special senses : abnormal visions, tinnitus

14 Overdose

Tenofovir Disoproxil Fumarate

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

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

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

Lamivudine

There is no known antidote for Lamivudine. One case of an adult ingesting 6 g of Lamivudine was reported; there were no clinical signs or symptoms noted and hematologic tests remained normal. Two cases of pediatric overdose were reported in Study ACTG300. One case involved a single dose of 7 mg/kg of Lamivudine; the second case involved use of 5 mg/kg of Lamivudine twice daily for 30 days. There were no clinical signs or symptoms noted in either case. Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event. If overdose occurs, the patient should be monitored, and standard supportive treatment.

Efavirenz

Some patients accidentally taking 600 mg twice daily have reported increased nervous system symptoms. One patient experienced involuntary muscle contractions. Treatment of overdose with Efavirenz should consist of general supportive measures, including monitoring of vital signs and observation of the patient's clinical status. Administration of activated charcoal may be used to aid

removal of unabsorbed drug. There is no specific antidote for overdose with Efavirenz. Since efavirenz is highly protein bound, dialysis is unlikely to significantly remove the drug from blood.

15 List of Excipients

a. Tablet core:
- Microcrystalline cellulose
- Croscarmellose Sodium
- Hydroxy propyl cellulose
- Sodium lauryl sulfate
- Ferric oxide
- Lactose monohydrate
- Magnesium stearate.

b. Tablet film coat:
Opadry II White 85F18422 (Polyvinyl alcohol, Titanium dioxide, Macrogol/PEG, Talc)

16 Incompatibilities

Not applicable

17 Storage

Do not store above 30°C. Store in the original package.
Keep out of reach and sight of children.

18 Shelf Life

24 months (2 years).
Use within 90 days after packaging opened.

19 Packaging Type and Size

Pack Type: HDPE bottle pack.
Pack size: 30’s

20. Manufactured by:

Mylan Laboratories Limited
Plot no: 11-12 & 13, Indore SEZ, Pharma Zone,
Phase-II, Sector-III, Pithampur – 454775
Dist. Dhar (MP) India.

Imported by:

PT. Kimia Farma (Persero) Tbk.
Jalan Rawa Gelam V No. 1
Pulo Kawasan Industri
Pulo Gadung Jakarta 13930
Jakarta – Indonesia

20 Classification of Drug

Obat Keras

21 Special Warning

Prescription Only
"HARUS DENGAN RESEP DOKTER"

Informasi Produk untuk Pasien
AVONZA
Tenofovir Disoproxil Fumarate / Lamivudine / Efavirenz
300 mg / 300 mg / 400 mg
Tablet Salut Selaput

Baca informasi ini secara lengkap dan seksama sebelum anda mulai menggunakan obat ini

- Simpan selebaran ini. Anda mungkin perlu membacanya lagi.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada Dokter atau Apoteker Anda.
- Obat ini hanya diresepkan untuk Anda. Jangan berikan kepada orang lain. Hal ini bisa membahayakan mereka, meskipun tanda atau gejala penyakitnya sama dengan Anda.
- Jika Anda mengalami efek samping, konsultasikan dengan Dokter atau Apoteker Anda. Termasuk kemungkinan efek samping yang tidak tercantum dalam selebaran ini. Lihat bagian 4.

Isi selebaran ini:

1. TENOFOVIR DISOPROXIL FUMARATE / LAMIVUDINE / EFAVIRENZ 300 MG / 300 MG / 400 MG DAN KEGUNAANNYA

Avonza mengandung Tenofovir Disoproxil Fumarate / Lamivudine / Efavirenz 300 mg/300 mg/400 mg Tablet yang digunakan sebagai pengobatan infeksi Human Immunodeficiency Virus-1 (HIV-1) pada pasien dewasa.

Avonza tidak dapat digunakan untuk anak dan remaja usia dibawah 18 tahun

2. YANG PERLU ANDA KETAHUI SEBELUM MENGGUNAKAN TENOFOVIR DISOPROXIL FUMARATE / LAMIVUDINE / EFAVIRENZ

Obat ini tidak mengurangi risiko penyebaran infeksi HIV melalui kontak seksual atau tranfusi darah.

Beritahu penyedia layanan kesehatan Anda jika Anda:

- Mengonsumsi obat lain yang mengandung tenofovir, lamivudine, atau efavirenz; analog sitidin (emtricitabine), adepovir dipivoksil, didanosin. Beritahu Dokter Anda daftar obat yang Anda konsumsi
- Mengalami gangguan fungsi fungsi hati, termasuk infeksi hepatitis B (HBV) dan hepatitis C (HCV)

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- Mengalami masalah ginjal
- Memiliki masalah tulang
- Memiliki kondisi medis lainnya, termasuk infeksi HIV
- Mengalami gangguan kejiwaan
- Mengalami gangguan jantung, termasuk perpanjangan interval QT
- Memiliki Riwayat Kejang
- Sebelum mengkonsumsi obat ini, beritahukan dokter Anda apabila ternyata Anda sedang hamil, atau menduga Anda sedang hamil, atau anda sedang berupaya untuk hamil. Anda harus menghindari kemungkinan hamil selama meminum Avonza sehubungan adanya risiko berbahaya pada bayi Anda.
- Untuk menghindari kemungkinan hamil selama meminum Avonza, Anda harus menggunakan kontrasepsi yang efektif selama pengobatan sampai sekurang-kurangnya 12 Minggu setelah pengobatan dengan Avonza berakhir.
- Anda tidak boleh menyusui jika Anda memiliki infeksi HIV atau AIDS. Virus yang menyebabkan HIV dapat menular ke bayi Anda lewat ASI. Konsultasikan dengan penyedia layanan kesehatan Anda mengenai cara terbaik untuk memberi makan bayi Anda.
- Anda tidak boleh menyetir atau mengoperasikan mesin saat menggunakan obat ini karena efek sampingnya.

Obat yang harus dihindari ketika mengonsumsi obat ini:

- Abacavir
- Emtricitabine
- Didanosin
- Nevirapin
- Etravirin
- Fosamprenavir
- Ritonavir
- Saquinavir
- Indinavir
- Lopinavir
- Atazanavir
- Tipranavir
- Darunavir
- Psaconazole
- Voriconazole
- Adepovir Dipivoxil
- Karbamazepin
- Fenitoin

Kenali obat yang Anda konsumsi. Simpan daftarnya untuk ditunjukkan kepada penyedia layanan kesehatan atau apoteker Anda saat Anda mendapatkan obat baru.

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3. CARA MENGGUNAKAN TENOFOVIR DISOPROXIL FUMARATE / LAMIVUDINE / EFAVIRENZ

Tenofovir Disoproxil Fumarate/Lamivudine/Efavirenz dikonsumsi sesuai dengan resep Dokter untuk pengobatan infeksi HIV-1. Dosis umum yang diberikan adalah 1 tablet Tenofovir Disoproxil Fumarate / Lamivudine / Efavirenz 300/300/400 mg satu kali sehari melalui rute oral dengan atau tanpa makanan.

4. KEMUNGKINAN EFEK SAMPING

Kemungkinan efek samping yang muncul saat penggunaan Tenofovir Disoproxil Fumarate / Lamivudine / Efavirenz adalah sebagai berikut:

Sistem Organ	Efek Samping (Frekuensi)
Gangguan Metabolik dan Nutrisi	• Peningkatan Trigliserida, Total Kolesterol, LDL, HDL, Hipofosfatemia (Sering) • Asidosis Laktat (Jarang) • Lipodistrofi, Hipokalemia (Tidak Diketahui)
Gangguan Sistem Peredaran Darah & Limfatik	• Neutropenia, Anemia, Trombositopenia (Jarang) • Aplasia (Sangat Jarang)
Gangguan Sistem Pernafasan, Toraks, dan Mediastinal	• Batuk, Gangguan Hidung (Sering) • Dispnea (Jarang)
Gangguan Sistem Saraf	• Pusing (Sangat Sering) • Mimpi Buruk, Gangguan Perhatian, Sakit Kepala, Insomnia, Somnolen (Sering) • Agitasi, Amnesia, Ataksia, Gangguan Koordinasi, Berpikir (Jarang) • Parastesia (Sangat Sering) • Tremor (Tidak Diketahui)
Gangguan Psikiatrik	• Ansietas, Depresi (Sering) • Gangguan Agresi, Mood, Halusinasi, Mania, Paranoid (Jarang) • Neurosis, Bunuh Diri (Tidak Diketahui)
Gangguan Hepatobilier	• Peningkatan Kadar Enzim Hati (Sering) • Hepatitis (Jarang) • Gagal Hati, Steatosis Hati (Tidak Diketahui)
Gangguan Ginjal & Sistem Urinaria	• Gagal Ginjal, Peningkatan Serum Kreatinin (Jarang) • Nekrosis Tubular Akut (Sangat Jarang) • Nefritis, Nefrogenik Diabetes Insipidus (Tidak Diketahui)
Gangguan Kulit dan Jaringan Subkutan	• Kemerahan (Sangat Sering) • Gatal, Rambut Rontok (Sering) • Eritema Multifform, Stevens-Johnson Sindrom (Jarang) • Dermatitis Fotoalergenik (Tidak Diketahui)
Gangguan Jaringan Penghubung dan Sistem Muskuloskletal	• Atralgia dan Mialgia (Sering) • Rhabdomyolisis, Osteomalasia, Otot Lemah, Miopati, Osteonekrosis (Tidak Diketahui)
Gangguan Sistem Reproduksi dan Payudara	Ginekomastia (Jarang)
Gangguan Mata	Rabun (Jarang)
Gangguan Telinga dan Sistem Keseimbangan	• Vertigo (Jarang) • Tinnitus (Tidak Diketahui)
Gangguan Umum	• Kelelahan, Mual, Muntah (Sering) • Ganggan Imun, *Flushing* (Tidak Diketahui)

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5. CARA MENYIMPAN AVONZA

- Simpan di bawah suhu 30°C dan terlindung dari cahaya.
- Simpan dalam wadah aslinya.
- Jangan konsumsi tablet Tenofovir Disoproxil Fumarat/Efavirenz/Lamivudine jika segel di atas bukaan botol rusak atau hilang.
- Jaga agar tutup botol tertutup rapat.
- Peringatan: Jauhkan dari jangkauan anak-anak.
- Gunakan dalam waktu 90 hari setelah kemasan dibuka.

6. ISI KEMASAN DAN INFORMASI LAIN

Tenofovir Disoproxil Fumarate / Lamivudine / Efavirenz Tablet Salut Selaput tersedia dalam Dus, Botol HDPE yang berisi 30 Tablet Salut Selaput.
Bahan tambahan yang digunakan antara lain:

a. Tablet Inti:
   - Mikrokristalin Selulosa
   - Natrium Kroskarmelosa
   - Hidroksipropil Selulosa
   - Natrium Lauril Sulfat
   - Ferro Oksida
   - Laktosa Monohidrat
   - Magnesium Stearat

b. Penyalut:
   Opadry II White 85F18422 (Polivinil Alkohol, Titanium Dioksida, Makrogol/PEG, Talkum)

Tenofovir Disoproxil Fumarate / Lamivudine / Efavirenz Tablet Salut Selaput dan Isi Kemasannya:
Tenofovir Disoproxil Fumarate / Lamivudine / Efavirenz Tablet Salut Selaput memiliki pemerian berupa tablet berwarna putih atau agak putih, bersalut selaput, oval, *beveled edge* dengan logo M pada satu sisi dan logo TLE pada sisi lainnya.

Nama & Alamat Pendaftar
PT. Kimia Farma – Plant Jakarta
Jl. Rawa Gelam V No.1
Kawasan Industri Pulogadung
Jakarta 13930

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Nama & Alamat Produsen
Mylan Laboratories Limited
Plot no: 11-12 & 13, Indore SEZ, Pharma Zone,
Phase-II, Sector-III, Pithampur – 454775
Dist. Dhar (MP) India.
Untuk informasi mengenai produk obat ini, hubungi pendaftar

"HARUS DENGAN RESEP DOKTER"

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