



<b>Mylan</b>				Date of Final	dd / mm / yy	Date of Issue	dd / mm / yy	Page Count	1 of 1
Date/Time of Creation	23/02/23 15:24	Track-Wise PR No.	NA	Client Market	Philippines	Software / Ver. No.	Adobe Illustrator 2021		
Vendor Job No.	NA	Affiliate New Code	NA	Product Description	CT TLE TAB 600/300/300MG 30'S PH				
Artwork Proof No.	NA	Aff. Superseded Code	NA	New Material Code	75095429	Actual A/w Size	64 x 54 x 92 mm		
Pharma Code	NA	Barcode Information	NA	ITF Barcode					
Product Render ID No.	NA	MA Number	NA	Superseded Code	NIL				
Main Font Type - 1	Helvetica Condensed	SAP or SPC Code	.....	Component Type	Printed Carton	Eye / Sensor Mark	NA		
Main Font Type - 2	.....	Packaging Site	Mylan Laboratories Ltd., FDF 3 (Pithampur, Dhar Dist., M.P. - IN)	No. of Printed Colors	4	ITF Barcode Size	NA		
Min. Font Size	7pt	Mfg. Lic. No. / Code No.	25/1/2014	Printed Colors CMYK / PMS Coated / PMS Color Bridge Coated	BLACK 100%	306 C	180 C	140 C	NA NA
Reason for Revision / Issuance	New Component	Non Printed Colors			Die Line	No Varnish	NA	NA	NA NA
Artwork Implementation Schedule, (✓) whichever is applicable	New Component	Equivalent with CMYK (Pantones Ref. Code)			NA				
	Immediately (Stock of superseded component to be destroyed, if applicable)	Material of Construction			270gsm ITC Cyber Plus Board with Spot Aqua Varnish				
	After Consumption of Existing (superseded) stock	Design & Style			Supply in Top open Reverse Tuck-In				
	Others (specify)	Prepared By			Checked By	Approved By			
Sign Offs	LABEL CONTROL / BUSINESS DEVELOPMENT / REGULATORY / MARKETING				Packaging Technical Services		Production	Regulatory Affairs	Quality Assurance
	Digital Signature	Digital Signature	Digital Signature	Digital Signature					
Revision History	31.01.2023 - New Component 16.02.2023 - Updation 22.02.2023 - Updation			23.02.2023 - Reg.No. Updation Date / Remarks Date / Remarks Date / Remarks			Date / Remarks Date / Remarks Date / Remarks Date / Remarks		

artwork - 100%

← Unwinding Direction

**Each film coated tablet contains:**  
 Efavirenz USP 600 mg  
 Lamivudine USP 300 mg  
 Tenofovir disoproxil fumarate 300 mg

Do not store above 30°C.  
 Store in the original container. Protect from light.  
**Dosage:** As directed by the physician.  
 NOT TO EXCEED THE PRESCRIBED DOSAGE.  
 KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

**Indications, Warnings & Precautions:**  
 Read the package leaflet before use.  
**Warning:** Formulation contains Lactose.  
**\*For suspected adverse drug reaction, report to the FDA: [www.fda.gov.ph](http://www.fda.gov.ph) and Faberco Life Sciences Inc. at: [safety@faberco.ph](mailto:safety@faberco.ph).**  
**Caution:** Foods, Drugs, Devices and Cosmetics  
 Act prohibits dispensing without prescription.  
 DRP-10882

**Efavirenz/Lamivudine/  
Tenofovir Disoproxil Fumarate**

**600 mg/300 mg/300 mg  
Film-Coated Tablet**

**Antiviral Combination**

**Rx**

30 Tablets

**Mylan**

**Imported and Distributed by**  
 Faberco Life Sciences Inc.,  
 2nd & 3rd Fl., One Armstrong Bldg.,  
 Armstrong Avenue Corner Yosemite St.,  
 Moonwalk, Paranaque City, Metro Manila


Mfg. Lic. No.: 25/1/2014  
 Manufactured by:  
**Mylan Laboratories Limited**  
 Plot No. 11,12 & 13, Indore SEZ, Pharma Zone,  
 Phase-II, Sector-III, Pithampur - 454775, Dist.-  
 Dhar (MP) India.



48x18 mm  
**Varnish Free Area  
for Coding**

**TO BE CODED ONLINE**

BATCH 1234567  
 MFD MMM YYYY  
 EXP MMM YYYY  
 (\*wherever is applicable)

				Date of Final	dd / mm / yy	Date of Issue	dd / mm / yy	Page Count	1 of 1	
Date/Time of Creation	23/02/23 15:22	Track-Wise PR No.	NA	Client Market	Philippines	Software / Ver. No.	Adobe Illustrator			
Vendor Job No.	NA	Affiliate New Code	NA	Product Description	LBST TLE TAB 600/300/300MG 30'S PH					
Artwork Proof No.	NA	Aff. Superseded Code	NA							
Pharma Code	NA	Barcode Information	NA	New Material Code	75095451	Actual A/w Size	117 x 40 mm			
Product Render ID No.	NA	MA Number	NA	ITF Barcode		Other Sizes (if any)	NA			
Main Font Type - 1	Helvetica Condensed	SAP or SPC Code	.....	Superseded Code	NIL	Pitch After Every	NA			
Main Font Type - 2	NA	Packaging Site	Mylan Laboratories Ltd., FDF 3 (Pithampur, Dhar Dist., M.P. - IN)	Component Type	Printed Self Adhesive Label	Eye / Sensor Mark	NA			
Min. Font Size	4.5pt	Mfg. Lic. No. / Code No.	25/1/2014	No. of Printed Colors	.....	ITF Barcode Size	NA			
Reason for Revision / Issuance	New Component			Printed Colors CMYK / PMS Coated / PMS Color Bridge Coated	BLACK 100%	306 C	180 C	140 C	NA	NA
	.....				Non Printed Colors	Die Line	No Varnish	NA	NA	NA
Artwork Implementation Schedule, (✓) whichever is applicable	New Component			Equivalent with CMYK (Pantones Ref. Code)	NA					
	Immediately (Stock of superseded component to be destroyed, if applicable)									
	After Consumption of Existing (superseded) stock			Material of Construction	80gsm Chromoart Paper + (62gsm Silicon Release Liner or 32gsm PET Release Liner) + 18gsm Adhesive with Spot Aqua Varnish					
Others (specify)			Design & Style	Supply In-Roll (Unwinding from Right to Left)						
<b>LABEL CONTROL / BUSINESS DEVELOPMENT / REGULATORY / MARKETING</b>				Prepared By	Checked By	Approved By				
Sign Offs				<b>Packaging Technical Services</b>		<b>Production</b>	<b>Regulatory Affairs</b>	<b>Quality Assurance</b>		
	Digital Signature	Digital Signature	Digital Signature	Digital Signature						
Revision History	31.01.2023 - Artwork Revised			Date / Remarks		Date / Remarks				
	16.02.2023 - Updation			Date / Remarks		Date / Remarks				
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				Date / Remarks		Date / Remarks				



## Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate

600mg/300mg/300mg Film-Coated Tablet

### Antiviral Combination

#### 1. NAME OF THE MEDICAL PRODUCT

Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets

#### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:  
Efavirenz 600 mg  
Lamivudine 300 mg  
Tenofovir disoproxil fumarate 300 mg (equivalent to tenofovir disoproxil 245 mg or tenofovir 136 mg)  
Each tablet contains 60 mg lactose monohydrate  
For a full list of excipients, see section 6.1

#### 3. PHARMACEUTICAL FORM

White colored, capsule shaped, film coated tablets debossed with "M 152" on one side and plain on other side. The tablets should not be divided.

#### 4. CLINICAL PARTICULARS

##### 4.1 Therapeutic indications

Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets is a fixed dose combination of tenofovir disoproxil fumarate, lamivudine and efavirenz. It is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and adolescents (from 12 years of age and weighing > 40 kg) with virologic suppression to HIV-1 RNA levels of < 50 copies/ml on their current combination antiretroviral therapy for more than three months. Patients must have experienced virological failure on any prior antiretroviral therapy.

The choice of Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets to treat antiretroviral experienced patients with HIV-1 infection should be based on individual viral resistance testing and/or the treatment history of the patient.

Consideration should be given to official treatment guidelines for HIV-1 infection (e.g. by WHO).

##### 4.2 Posology and method of administration

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

##### Posology

Adults and adolescents: the recommended dose of Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets is one tablet taken orally once daily.

##### Method of administration

It is recommended that Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets be swallowed whole with water.

It is recommended that Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets be taken on an empty stomach since food may increase efavirenz exposure and may lead to an increase in the frequency of adverse reactions (see sections 4.4 and 4.8).

In order to improve the tolerability of efavirenz with respect to undesirable effects on the nervous system, bedtime dosing is recommended (see section 4.8).

It is anticipated that tenofovir exposure will be approximately 35% lower following administration of Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets on an empty stomach as compared to the individual component tenofovir disoproxil fumarate when taken with food (see section 5.2). In virologically suppressed patients, the clinical relevance of this reduction is expected to be limited (see section 5.1).

##### Children

Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets is not recommended for use in children below 12 years of age due to a lack of data on safety and efficacy.

##### Elderly

Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets should be administered with caution to elderly patients (see section 4.4).

##### Dose adjustments

Where discontinuation of therapy with one of the components of Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets is necessary, separate dosing regimens for each component should be used. Separate dosing regimens for each component are available. Please refer to the Summary of Product Characteristics for these medicinal products.

Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets is co-administered with rilpivirine, an additional 200 mg/day (800 mg total) of efavirenz may be considered (see section 4.5).

##### Renal impairment

Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets is not recommended for patients with moderate or severe renal impairment (creatinine clearance (CrCl) < 50 ml/min). Patients with moderate or severe renal impairment require dose interval adjustment of lamivudine and tenofovir disoproxil fumarate that cannot be achieved with the combination tablet (see sections 4.4 and 5.2).

##### Hepatic impairment

The pharmacokinetics of Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets have not been studied in patients with hepatic impairment. Patients should be monitored carefully for adverse reactions, especially nervous system symptoms (see sections 4.3 and 4.4).

If Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets is discontinued in patients co-infected with HIV and HBV, these patients should be closely monitored for evidence of exacerbation of hepatitis (see section 4.4).

If therapy with Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets is discontinued, consideration should be given to the long half-life of efavirenz (see section 5.2) and long intracellular half-lives of tenofovir and lamivudine. Because of interpatient variability in these parameters and concerns regarding development of resistance, HIV treatment guidelines should be consulted, also taking into consideration the nature of discontinuation.

#### 4.3 Contraindications

Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets is contraindicated in patients with clinically significant hypersensitivity to tenofovir, lamivudine, or efavirenz or to any of the excipients contained in the formulation.

Herbal preparations containing St. John's wort (*Hypericum perforatum*) must not be used while taking Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets due to the risk of decreased plasma concentrations and reduced clinical effects of efavirenz (see section 4.5).

Efavirenz significantly decreases voriconazole plasma concentrations while voriconazole also significantly increases efavirenz plasma concentrations. Since Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets is a fixed-dose combination product, the dose of efavirenz cannot be altered; therefore, voriconazole and Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets must not be co-administered (see section 4.5).

#### 4.4 Special warnings and precautions for use

##### General

As a fixed combination, Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets should not be administered concomitantly with other medicinal products containing any of the same active components, efavirenz, lamivudine or tenofovir disoproxil fumarate. Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets should not be administered concomitantly with other cytidine analogues such as entricarbazine (see section 4.5). Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets should not be administered concomitantly with didanosine dipivaloxil.

##### Transmission of HIV

Treatment with Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets has not been shown to eliminate the risk of transmission of HIV infection by sexual contact or by blood transfer, although the risk may be reduced. Patients should continue to use appropriate precautions to prevent transmission of HIV.

**Didanosine**  
Co-administration of Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets and didanosine is not recommended since exposure to didanosine is significantly increased following co-administration with tenofovir disoproxil fumarate (see section 4.5).

##### Liver disease

The safety and pharmacokinetics of efavirenz has not been investigated in patients with severe liver disease. Therefore Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets should only be used in this group of patients if the benefits are considered to outweigh the risks, and with close safety monitoring.

##### Liver toxicity

Increased transaminase levels may occur months after starting efavirenz and may be more frequent in patients with HIV- and/or HCV co-infection. Discontinuation is recommended if hepatotoxicity is symptomatic, or if the transaminase levels are > 10 times the upper limit of normal.

Hepatic failure has occurred in patients with no preexisting hepatic disease or other identifiable risk factors (see section 4.8). Liver enzyme monitoring should be considered for patients without preexisting hepatic dysfunction or other risk factors.

##### Patients with HIV and hepatitis B (HBV) or C virus (HCV) co-infection

Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. Physicians should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with HBV.

Lamivudine and tenofovir disoproxil fumarate are also active against HBV. Therefore, discontinuation of Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis. Patients co-infected with HIV and HBV who discontinue Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets must be closely monitored with both clinical and laboratory follow-up for at least four months after stopping treatment with Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets. If appropriate, resumption of specific anti-hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

##### Rash

A mild-to-moderate rash very commonly develops within two weeks after starting efavirenz and does not require treatment discontinuation. The rash usually resolves within two weeks. Severe rash or erythema, including Stevens-Johnson syndrome, requires immediate discontinuation (see section 4.8).

##### Central nervous system and psychiatric effects

Central nervous system and psychiatric side effects are very common after starting efavirenz (see section 4.8). These symptoms typically occur within the first week of treatment and usually resolve within two weeks of treatment. There is a potential additive effect with alcohol and other psychoactive drugs. Patients should be advised that if they experience symptoms such as severe depression, psychosis or suicidal ideation they should contact their doctor or health care provider immediately to determine whether the benefits outweigh the risks of continued therapy.

##### Renal function

Tenofovir is primarily excreted by the kidneys through a combination of glomerular filtration and active tubular secretion. Thus, clearance is decreased in patients with impaired renal function. There are limited data on the safety and efficacy of tenofovir disoproxil fumarate in patients with impaired renal function (< 80 ml/min). In such patients, Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets should only be used if the potential benefits of treatment are considered to outweigh the potential risks.

In patients with moderate to severe renal impairment, the plasma half-life of lamivudine is increased due to decreased clearance. Decreased doses are recommended for patients with creatinine clearance < 50 ml/min. The use of Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets is not recommended in patients with creatinine clearance < 50 ml/min, since appropriate dose reductions cannot be achieved with the combination tablet (see sections 4.2 and 5.2).

Renal failure, renal impairment, elevated creatinine, hypophosphatemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir disoproxil fumarate in clinical practice (see section 4.8). It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets. Routine monitoring of calculated creatinine clearance and serum phosphate should be performed in patients at risk for renal impairment.

In patients receiving tenofovir disoproxil fumarate renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations, if serum phosphate is < 1.5 mg/dl (0.48 mmol/l) or creatinine clearance decreases below 50 ml/min (see section 4.8, proximal tubulopathy).

Consideration should also be given to interrupting treatment with Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets in patients whose creatinine clearance falls below 50 ml/min or whose serum phosphate decreases below 1.0 mg/dl (0.32 mmol/l).

Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets should be avoided with concurrent use of a nephrotoxic medicinal product (e.g. aminoglycosides, amphotericin B, fosfomic acid, gentamicin, pentamidine, vancomycin, cidofovir or interferon-2). If concomitant use of tenofovir disoproxil fumarate and nephrotoxic agents is unavoidable, renal function should be monitored weekly.

##### Bone effects

In a controlled clinical study decreases in bone mineral density of spine and changes in bone biomarkers from baseline were observed in both treatment groups, but were significantly greater in the tenofovir disoproxil fumarate treatment group than in the comparator group treated with stavudine (each in combination with lamivudine and efavirenz) at 144 weeks. Decreases in bone mineral density of hip were significantly greater in this group until 96 weeks. However, there was no increased risk of fractures or evidence for clinically relevant bone abnormalities over 144 weeks.

Tenofovir was studied in HIV-1 infected paediatric subjects 12 years of age and older. Under normal circumstances, bone mineral density increases rapidly in this age group. In this study, the mean rate of bone gain was less in the tenofovir-treated group compared to the placebo group. Skeletal growth (height) appeared to be unaffected. Markers of bone turnover in tenofovir-treated paediatric subjects 12 years of age and older suggest increased bone turnover, consistent with the effects observed in adults. Due to the possible effects of tenofovir on bone metabolism, Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets should only be used in adolescents under the age of 18 if the benefits are considered to exceed the risk (see also section 4.8).

Bone abnormalities (frequently contributing to fractures) may be associated with proximal renal tubulopathy (see section 4.8). If bone abnormalities are suspected then appropriate consultation should be obtained.

##### Lactic acidosis

Lactic acidosis is a rare but severe, potentially life-threatening complication associated with use of nucleoside reverse transcriptase inhibitors (NRTI). Several other agents of this class are known to cause lactic acidosis. Preclinical and clinical data suggest that the risk of occurrence of lactic acidosis, considered a putative class effect of nucleoside analogues, is very low for tenofovir disoproxil fumarate and lamivudine. However, the risk cannot be excluded. Lactic acidosis may occur after a few to several months of NRTI treatment. Patients with hyperlactatemia may be asymptomatic, critically ill, or may have non-specific symptoms such as dyspnoea, fatigue, nausea, vomiting, diarrhoea and abdominal pain. Risk factors for NRTI-related lactic acidosis include female gender and obesity. Patients at increased risk should be closely monitored clinically. Screening for hyperlactatemia in asymptomatic patients treated with NRTIs, however, is not recommended. Symptomatic patients usually have levels > 5 mmol/l and require discontinuation of all NRTIs. Lactic acid levels > 10 mmol/l usually are a medical emergency.

##### Lipodystrophy and metabolic disorders

Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV-infected patients. Whereas for some other antiretrovirals there is considerable evidence for this adverse reaction, the evidence for tenofovir, lamivudine and efavirenz as causative agents is weak, indeed switching from a thymidine analogue (e.g. stavudine) to tenofovir has been shown to increase fat in patients with lipodystrophy. A higher risk of lipodystrophy has been associated e.g. with older age of the patient, longer duration of antiretroviral therapy and related metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Measurement of fasting serum lipids and blood glucose as well as appropriate management of lipid disorders should be considered (see section 4.8).

##### Mitochondrial dysfunction

Nucleoside and nucleotide analogues have been demonstrated, *in vitro* and *in vivo*, to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV negative infants exposed *in utero* and/or postnatally to nucleoside analogues. The main adverse events reported are haematological disorders (anaemia, neutropenia), renal and metabolic disorders (hyperlactatemia, hypoglycaemia). These events are often transient. Some late-onset neurological disorders have been reported (hyperreflexia, convulsion, abnormal behaviour). Whether the neurological disorders are transient or permanent is currently unknown. Any child exposed *in utero* to nucleoside and nucleotide analogues, even HIV-negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. These findings do not affect current national recommendations to use combination antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

##### Pancreatitis

Treatment with Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets should be stopped immediately if clinical signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur (see section 4.8).

##### Opportunistic infections

Patients receiving antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection that require clinical observation by a physician or health care providers experienced in the treatment of HIV infection.

##### Immune Reactivation Syndrome

In HIV-infected patients with pre-existing severe immune deficiency, typically in the first few weeks or months after initiation of combination ART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens (e.g. CMV retinitis, mycobacterial infections, Pneumocystis pneumonia) may arise and cause serious clinical conditions or aggravation of symptoms. Treatment should be instituted when necessary.

##### Diposone

Although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported, particularly in patients with advanced HIV disease and/or long-term exposure to antiretroviral therapy. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

##### Elderly patients

Elderly patients are more likely to have decreased renal function; therefore caution should be exercised when treating elderly patients with tenofovir disoproxil fumarate (see section 4.4).

##### Excipients

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose/galactose malabsorption should not take this medicine. This medicinal product contains 1.9 mmol (43 mg) sodium per tablet. To be taken into consideration by patients on controlled sodium diet.

#### 4.5 Interaction with other medicinal products and other forms of interaction

##### Interactions relevant to lamivudine

Co-administration with trimethoprim / sulfamethoxazole results in a 40% increase in lamivudine area under the concentration curve. No dose adjustment of Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets is necessary. Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole.

##### Interactions relevant to tenofovir Disoproxil Fumarate

Co-administration of tenofovir disoproxil fumarate and didanosine is not recommended (see section 4.4 and the table below).

##### Renally eliminated medicinal products

Since tenofovir is primarily eliminated by the kidneys, co-administration of tenofovir disoproxil fumarate with medicinal products that reduce renal function or compete for active tubular secretion (transport proteins: HAT1, HAT2 3 or MRP 4 or MRP 4 or C19orf15) may increase serum concentrations of tenofovir and/or the co-administered medicinal products.

Tenofovir disoproxil fumarate should be avoided with concurrent use of a nephrotoxic medicinal product, such as aminoglycosides, amphotericin B, fosfomic acid, gentamicin, pentamidine, vancomycin, cidofovir or interferon-2 (see section 4.4).

Given that tenofovir can affect renal function, close monitoring is recommended when it is co-administered with tenofovir disoproxil fumarate.

##### Interactions relevant to efavirenz

Efavirenz is eliminated through hepatic metabolism, mainly catalyzed by the genetically polymorphic cytochrome (CYP) 450 isozyme CYP2B6, but also by CYP3A4. Therefore, agents that alter the activity of CYP2B6 or CYP3A4 may alter the plasma concentration of efavirenz.

Efavirenz is a clinically important inducer of cytochrome P450 enzymes, such as CYP3A4. Therefore interactions with medicinal products metabolized by this pathway may occur. *In vitro*, efavirenz is also an inhibitor of UDP-glucosyl transferases, CYP3A4, CYP2C9 and CYP2C19. In the great majority of cases where efavirenz interacts *in vivo* with known CYP3A4 substrates, the net result after multiple doses is a decreased systemic exposure of the drug interacting with efavirenz. Though efavirenz might act *in vivo* as a net inhibitor of CYP3A4 after the first doses, it has not been demonstrated that this happens since CYP3A4 induction has set in.

Efavirenz should not be administered concurrently with terfenadine, astemizole, cisapride, pimozide, bepridil or ergot derivatives, since this may result in altered plasma concentrations of these drugs.

**Table of drug interactions for Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets.**

The following list of interactions should not be considered exhaustive, but as representative of the classes of medicinal products where caution should be exercised (increased exposure is indicated as "+", decreased exposure as "-", no change as "=", three daily as "t.i.d.", twice daily as "b.i.d.", and once daily as "o.d.").

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration
<b>ANTI-INFECTIVES</b>		
<b>Antiretrovirals</b>		
Nucleoside analogues <b>Zidovudine</b> <b>Stavudine</b> <b>Abacavir / tenofovir</b>	No interaction expected	
Entricitabine / lamivudine	Entricitabine and Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets should not be co-administered, due to the similarity between entricarbazine and lamivudine, and consequently expected lack of additive effects (see section 4.4).	
Didanosine (400 mg q.d.) / tenofovir	Didanosine AUC ↑ 40-60%	The risk of didanosine-related adverse effects (e.g. pancreatitis, lactic acidosis) appears to be increased, and CD4 cells may decrease significantly on co-administration. Also didanosine at 250 mg co-administered with tenofovir within several different antiretroviral combination regimens has been associated with a high rate of virological failure. Co-administration of Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets and didanosine is not recommended (see section 4.4).
Non-nucleoside inhibitors of reverse transcriptase <b>Nevirapine</b> <b>Etravirine</b>	Concomitant use with Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets is not recommended because of additive toxicity and no benefit in terms of efficacy.	
Protease inhibitors		
Fosamprenavir / ritonavir (700/100 mg b.i.d.) / efavirenz	amprenavir C trough ↓ 17%. No significant interaction with twice daily regimen at steady state	No dose adjustment necessary.
Fosamprenavir / ritonavir (1400/200mg q.d.) / efavirenz	amprenavir C trough ↓ 36% at steady state	Avoid concomitant use of Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets and once-daily fosamprenavir regimen.
Saguinavir HCl/ritonavir (1000/100mg b.i.d.) / efavirenz	No clinically relevant interaction was noted.	Insufficient data are available for making a dosing recommendation for saquinavir, with or without ritonavir, when co-administered with Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets. Co-administration with saquinavir, with or without ritonavir, is not recommended.
Indinavir (800 mg t.i.d.) / efavirenz	Indinavir AUC ↓ 31%, C trough ↓ 40%	Concomitant use of Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets with unboosted indinavir is not recommended.
Indinavir/ritonavir (800/100 mg b.i.d.) / efavirenz	Indinavir AUCs ↓ 25%, C trough ↓ 50%	Concomitant use of Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets with boosted indinavir is only recommended when it is possible to monitor the plasma concentration of indinavir.
<b>Antibacterials/Antifungal/antiparasitics</b>		
Clarithromycin (500 mg b.i.d, multiple doses) / efavirenz	Clarithromycin AUC ↓ 39%, 14-OH-clarithromycin AUC ↑ 34%	The clinical significance, if any, of these alterations in clarithromycin exposure are not known. A high frequency of rash was seen when the drugs were co-administered in healthy volunteers. Consider azithromycin instead, if possible.
Azithromycin (600 mg single dose) / efavirenz (400 mg once daily)	No clinically significant pharmacokinetic interaction	No dosage adjustment is necessary for either medicinal product
Rifampicin (600 mg q.d, multiple doses) / efavirenz	Efavirenz AUC ↓ 26%, C trough ↓ 32%	When co-treating, a dose increase of efavirenz should be considered.
Rifabutin (300 mg q.d.) / efavirenz	Rifabutin AUCs ↑ 38%	Increase rifabutin dose by 50% if co-treating with
<b>Antimicrobials</b>		
Aloquone <b>Chloroquine</b> <b>Mefloquine</b> <b>Progammil</b> <b>Sulfadoxine</b> <b>Pyrimethamine / efavirenz</b>	No formal interaction studies available. Drug - drug interactions and safety in co-administration with efavirenz has not been systematically evaluated, on a theoretical basis, clinically significant drug interactions with efavirenz are unlikely.	If co-administration is considered necessary, rifampicin should be dosed 400 mg b.i.d. and rifabutin dosed at 300 mg q.d. As this dose reduction of efavirenz cannot be accommodated for with Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets, alternative formulations of efavirenz, tenofovir and lamivudine should be used (see section 4.3).
<b>Amodiaquine / artesunate (600/250 mg q.d.) / efavirenz</b>	An interaction study (EFV at steady-state) was terminated after the first two subjects developed asymptomatic but significant hepatic enzyme elevations after a three-day course of amodiaquine. Amodiaquine AUC: T 114 and 302% respectively	Possibly increased hepatic toxicity. Avoid combination.
<b>ANTIMETABOLITES/AGENTS/HEAVY METALS</b>		
Adefovir dipivoxil / tenofovir	AUC: ↔ C trough: ↔	Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets should not be administered concurrently with adefovir dipivoxil due to an expected lack of additive effect (see section 4.4).
Entecavir (1 mg q.d.)	AUC: ↔ C trough: ↔	No clinically significant pharmacokinetic interactions when Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets is co-administered with entecavir.



ANTICOVULSANTS		
<b>Carbamazepine</b> (400 mg q.d.) / efavirenz	Carbamazepine AUCs: ↓ 27%, C <sub>min</sub> ↓ 30% efavirenz AUCs: ↓ 36%, C <sub>min</sub> ↓ 47%	Co-administration should be avoided unless plasma concentrations of carbamazepine and efavirenz can be monitored.
<b>Phenytoin</b> / efavirenz	No interaction study available Phenytoin and efavirenz clearance is likely to be increased.	Co-administration should be avoided unless plasma concentrations of carbamazepine and efavirenz can be monitored.
<b>Valproic acid</b> (250 mg b.i.d.) / efavirenz	No significant interaction is likely.	
<b>Vigabatrin</b>	No significant interaction is likely	Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets and vigabatrin can be coadministered without dose adjustment.
CARDIOVASCULAR AGENTS		
Calcium channel blockers		
<b>Diltiazem</b> (240 mg q.d.) / efavirenz	Diltiazem: AUC: ↓ 69% Desacetyl diltiazem: AUC: 175% N-desmethyl diltiazem: AUC: ↓ 37%	Monitor the clinical effect of diltiazem and increase dose if necessary.
<b>Verapamil, Nifedipine, nifedipine, nicardipine / efavirenz</b>	Interaction not studied. Calcium channel blocker exposure is likely to be lowered in cotreatment with efavirenz.	Monitor clinical effect and increase calcium channel blocker dose if necessary.
LIPID LOWERING AGENTS		
<b>Atorvastatin</b> (10 mg q.d.) / efavirenz	Atorvastatin: AUC: ↓ 43% Total active moiety AUC: ↓ 34%	Cholesterol levels should be periodically monitored and the dose of atorvastatin increased in case of insufficient efficacy.
<b>Pravastatin</b> (40 mg q.d.) / efavirenz	Pravastatin: AUC: ↓ 40%	Cholesterol levels should be periodically monitored and the dose of pravastatin increased in case of insufficient efficacy.
<b>Simvastatin</b> (40 mg q.d.) / efavirenz	Simvastatin: AUC: ↓ 69% Total active moiety: AUC: ↓ 60%	Cholesterol levels should be periodically monitored and the dose of simvastatin increased in case of insufficient efficacy.
<b>Ezetimibe</b> / efavirenz	Interaction not studied. Rosuvastatin is largely excreted unchanged via the faeces; therefore metabolic drug interaction with efavirenz is not expected.	
HORMONAL CONTRACEPTIVES		
<b>Ethinylestradiol norgestimate</b> (0.035 mg + 0.25 mg q.d.) / efavirenz	No change in ethinylestradiol exposure. Levonorgestrel AUC: ↓ 83% Norgestimate AUC: ↓ 64% (active metabolites).	A reliable method of barrier contraception should be used in addition to oral contraceptives.
<b>DMPA</b> (150 mg i.m. single dose) / efavirenz	The pharmacokinetics and efficacy of DMPA was not altered due to co-treatment with efavirenz.	Because of the limited information available, a reliable method of barrier contraception must be used in addition to hormonal contraception.
<b>Etonogestrel</b> (implant) / efavirenz	Interaction not studied. Decreased exposure of etonogestrel may be expected due to the CYP3A4 induction of efavirenz. There have been occasional postmarketing reports of contraceptive failure with etonogestrel in efavirenz-treated patients.	A reliable method of barrier contraception must be used in addition to hormonal contraception.
IMMUNOSUPPRESSANTS		
<b>Tacrolimus, cyclosporine, sirolimus / efavirenz</b>	Interaction not formally studied. Decreased exposure of these immunosuppressants may be expected when co-treating with efavirenz.	Dose adjustments of the immunosuppressants may be needed. Close monitoring of immunosuppressant drug concentrations for at least 2 weeks (until steady-state concentrations are reached) is recommended when starting or stopping therapy with Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets.
OTHERS		
<b>Methadone</b> / efavirenz	Methadone AUC: ↓ 52%	Monitor for withdrawal symptoms and increase methadone dose if necessary.
<b>Buprenorphine</b> / efavirenz	Buprenorphine AUC: ↓ 50%; not buprenorphine: ↓ 71% (active metabolite) Despite these decreases in exposure, no patients in the study exhibited withdrawal symptoms.	Monitor for withdrawal symptoms and increase buprenorphine dose if necessary.
<b>Warfarin</b> / efavirenz	No interaction study available Co-administration may decrease (and less likely increase warfarin exposure).	Monitor INR. Dose adjustments of warfarin may be necessary.
<b>Lorazepam</b> (2mg single dose) / efavirenz	Lorazepam: AUC: ↑ 7% (↑ to ↓ 14)	No dose adjustment necessary
<b>Midazolam, Zolozepam</b> / efavirenz	No interaction study available	These benzodiazepines are metabolized by CYP3A. While efavirenz is an inducer of CYP3A in vivo, it acts as an inhibitor <i>in vitro</i> . The impact of co-administration on midazolam and zolozepam pharmacokinetics is unknown. Co-administer with caution.
<b>St. John's Wort (Hypericum perforatum) / efavirenz</b>	No interaction study available	Concomitant treatment contraindicated. Coadministration likely to decrease efavirenz levels and to precipitate neurological failure.

#### 4.6 Pregnancy and lactation

##### Women of childbearing potential:

Based on the animal data, it is recommended that pregnancy should be avoided in women treated with efavirenz, one of the components of Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets. Barrier contraception should always be used in combination with other methods of contraception (for example, 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/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets.

##### Pregnancy:

Studies of efavirenz in animals have shown reproductive toxicity, including marked teratogenic effects (see section 5.3). Cases of neural tube defects in infants born to women with first trimester exposure have been reported. The postmarketing data available ([www.aars.gov.sg](http://www.aars.gov.sg)) including sufficient pregnancies to exclude a twofold increase from baseline, does not demonstrate an increased number of malformations in mothers exposed to efavirenz, nor any specific pattern of malformations. Efavirenz should not be used during the first trimester of pregnancy. Animal studies do not indicate direct or indirect harmful effects of tenofovir disoproxil fumarate with respect to pregnancy, foetal development, parturition or postnatal development (see section 5.3). In humans, the safety of tenofovir in pregnancy has not been fully established. Sufficient numbers of first trimester exposures have been monitored, however, to detect at least a twofold increase in the risk of overall birth defects. No increase in birth defects was seen ([www.aars.gov.sg](http://www.aars.gov.sg)).

No increased risk of birth defects has been reported for lamivudine ([www.aars.gov.sg](http://www.aars.gov.sg)). However, risks to the fetus cannot be ruled out. Due to the possible teratogenic effects of efavirenz, Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets should not be used during the first trimester of pregnancy, and only used during the subsequent trimester if the benefit is considered to outweigh the risk.

##### Breast-feeding:

In animal studies it has been shown that tenofovir is excreted into milk. It is not known whether tenofovir is excreted in human milk. Lamivudine is excreted into the breast milk of lactating mothers. It is not known whether efavirenz is excreted in human milk. Current recommendations on HIV and breastfeeding (e.g. those from the WHO) should be consulted before advising patients on this matter. Preferred options may vary depending on the local circumstances.

##### 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, dizziness has been reported during treatment with efavirenz and tenofovir disoproxil fumarate. Efavirenz may also cause impaired concentration if the benefit is considered to outweigh the risk. 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 controlled clinical trials during treatment of HIV-1 infection with efavirenz, lamivudine and/or tenofovir disoproxil fumarate.

The adverse events considered at least possibly related to the treatment are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000). In addition, adverse events identified during post-approval use are listed (frequency category: 'not known'). Since they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been included for their potential causal connection to the active components of Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets, taking also into account their seriousness and the number of reports.

##### Metabolic and nutrition disorders

**Very common:** increases in fasting triglycerides, total cholesterol, high- and low-density lipoprotein cholesterol, hypophosphataemia  
**Rare:** lactic acidosis  
**Not known:** hypodystrophy, hypokalaemia

##### Blood and lymphatic systems disorders

**Uncommon:** neutropenia, anaemia, thrombocytopenia  
**Very rare:** pure red cell aplasia  
**Respiratory, thoracic and mediastinal disorders**  
**Common:** cough, nasal symptoms  
**Very rare:** dyspnoea

##### Nervous system disorders

**Very common:** dizziness  
**Common:** abnormal dreams, disturbance in attention, headache, insomnia, somnolence.  
**Uncommon:** agitation, amnesia, ataxia, abnormal coordination, confusional state, convulsions, abnormal thinking  
**Very rare:** peripheral neuropathy (paresthesiae) **Not known:** tremor

##### Psychiatric disorders

**Common:** anxiety and depression  
**Uncommon:** affect lability, aggression, euphoric mood, hallucination, mania, paranoia, suicide attempt, suicidal ideation  
**Not known:** neurosis, completed suicide  
**Very rare:** depression

##### Hepatobiliary disorders

**Common:** elevation of liver enzymes  
**Uncommon:** acute hepatitis  
**Not known:** hepatic failure, hepatic steatosis

##### Renal and urinary disorders:

**Rare:** acute renal failure, renal failure, proximal renal tubulopathy (including Fanconi syndrome), increased serum creatinine  
**Very rare:** acute tubular necrosis  
**Unkown:** nephritis (including acute interstitial nephritis), nephrogenic diabetes insipidus

##### Skin and subcutaneous tissue disorders

**Very common:** rash  
**Common:** pruritus, hair loss  
**Uncommon:** erythema multiforme, Stevens-Johnson syndrome  
**Not known:** photoallergic dermatitis

##### Musculoskeletal and connective tissue disorders

**Common:** arthralgia, myalgia  
**Not known:** rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), muscular weakness, myopathy, osteonecrosis (see section 4.4)  
**Reproductive system and breast disorders**  
**Uncommon:** gynecomastia

##### Eye disorders

**Uncommon:** blurred vision

##### Ear and labyrinth disorders

**Uncommon:** vertigo  
**Not known:** tinnitus

##### Gastrointestinal disorders

**Very common:** diarrhoea, nausea, vomiting  
**Common:** abdominal pain, flatulence  
**Uncommon:** acute pancreatitis

##### General disorders and administration site disorders

**Common:** fatigue, malaise, fever  
**Not known:** immune-mediated syndrome (see section 4.4), flushing

##### Description of selected adverse reactions

###### Renal tubulopathy

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy due to tenofovir disoproxil fumarate: rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), hypokalaemia, muscular weakness, myopathy and hypophosphataemia. These events are not considered to be causally associated with Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets therapy in the absence of proximal renal tubulopathy.

###### Nervous system symptoms

Nervous system symptoms are common with efavirenz, one of the components of Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets. In clinical controlled studies of efavirenz, nervous system symptoms of moderate to severe intensity were experienced by 19% (severe 2%) of patients, and 2% of patients discontinued therapy due to such symptoms. They usually begin during the first one or two days of efavirenz therapy and generally resolve after the first two to four weeks. They may occur more frequently when Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets is taken concomitantly with meals possibly due to increased efavirenz plasma levels (see section 5.2). Dosing at bedtime seems to improve the tolerability of these symptoms (see section 4.2).

###### Bone effects of tenofovir in adolescents

The effect of tenofovir on bone mass in those not fully grown is a specific theoretical safety concern. Assessment of adverse reactions is based on one randomized trial in 97 HIV-1 infected paediatric subjects (12 to <18 years of age) who received treatment with tenofovir (N=45) or placebo (N=42) in combination with other antiretroviral agents for 48 weeks. Bone effects observed in paediatric subjects 12 years of age and older, such as increased bone turnover were consistent with those observed in adult clinical trials (see section 4.4).

###### 4.9 Overdose

If overdose occurs the patient must be monitored for evidence of toxicity (see sections 4.8 and 5.3), and standard supportive treatment applied as necessary). Some patients accidentally taking efavirenz 800 mg twice daily have reported increased nervous system symptoms. One patient experienced involuntary muscle contractions. Administration of activated charcoal may be used to aid removal of unabsorbed efavirenz. There is no specific antidote for overdose with efavirenz. Since efavirenz is highly protein bound, dialysis is unlikely to remove significant quantities of it from blood. Tenofovir can be removed by haemodialysis; the median haemodialysis clearance of tenofovir is 134 ml/min. The elimination of tenofovir by peritoneal dialysis has not been studied.

Because a negligible amount of lamivudine was removed via 4-hour haemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous haemodialysis would provide clinical benefit in a lamivudine overdose event.

##### 5. PHARMACOLOGICAL PROPERTIES

###### 5.1 Pharmacodynamic properties

Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets for treatment of HIV infections, combinations, ATC code: J05AR

**Mechanism of action and pharmacodynamic effects:** Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. Efavirenz binds directly to reverse transcriptase and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by inducing a conformational change that causes a disruption of the enzyme's catalytic site. The activity of efavirenz does not compete with template or nucleoside triphosphates. HIV-2 reverse transcriptase and eukaryotic DNA polymerases (such as human DNA polymerases α, β, γ, or θ) are not inhibited by efavirenz.

Lamivudine, the negative enantiomer of 2'-deoxy-3'-thiathymidine, is a dideoxynucleoside analogue. Tenofovir disoproxil fumarate is converted *in vivo* to tenofovir, a nucleoside monophosphate (nucleotide) analogue of deoxosine monophosphate. Lamivudine and tenofovir are phosphorylated by cellular enzymes to form lamivudine triphosphate and tenofovir diphosphate, respectively. Lamivudine triphosphate and tenofovir diphosphate competitively inhibit HIV-1 reverse transcriptase (RT), resulting in DNA chain termination. Both substances are active against HIV-1 and HIV-2, as well as against hepatitis B virus.

###### Resistance:

A large proportion of patients experiencing virological failure while receiving efavirenz will develop resistance to efavirenz. The main mutations occurring are K103N/E and Y188L, a single one of these mutations is sufficient to cause high-grade resistance. The cross resistance between efavirenz and nevirapine or delamanvir is extensive; therefore patients who have experienced virological failure with either of these drugs, are likely to harbor virus not susceptible to efavirenz, and vice versa. With an accumulating number of NNRTI mutations, the susceptibility to efavirenz will also be compromised.

Due to the long half-life of efavirenz, a period of functional monotherapy with efavirenz may follow upon discontinuation of effective efavirenz-containing antiretroviral therapy. This may cause significant resistance and compromise the efficacy of future efavirenz, nevirapine or delamanvir therapy (see section 4.4).

In many cases when a lamivudine-containing treatment regimen fails, the M184V mutation will be selected for at an early stage. M184V causes high-level resistance to lamivudine (>300-fold reduced susceptibility). Virus with M184V replicates less well than does wild type virus. M184V causes high-level resistance to lamivudine (>300-fold reduced susceptibility).

*In vivo* data tend to suggest that the continuation of lamivudine in an antiretroviral regimen despite the development of M184V might provide residual anti-retroviral activity (likely through impaired viral fitness). The clinical relevance of these findings is not established.

Cross-resistance conferred by the M184V mutation is limited within the nucleoside/nucleotide inhibitor class. Antiretroviral agents, M184V confers full cross-resistance against emtricitabine, didanosine and stavudine maintain their antiretroviral activities against lamivudine-resistant HIV-1. Abacavir maintains its antiretroviral activities against lamivudine-resistant HIV-1 harbouring only the M184V mutation. The M184V mutation confers a 4-4-fold decrease in susceptibility to didanosine; the clinical significance of this is unknown.

The K65R mutation is selected *in vitro* when HIV-1 is cultured in the presence of increasing tenofovir concentrations. It may also emerge *in vivo* upon virological failure of a treatment regimen including tenofovir. K65R reduces tenofovir susceptibility *in vitro* approximately 2-fold, and has been associated with a lack of response to tenofovir-containing regimens.

Clinical studies in treatment-experienced patients have assessed the anti-HIV activity of tenofovir against strains of HIV-1 with thymidine analogue mutations (TAMs), which are not selected for by tenofovir. Patients whose HIV expressed 3 or more TAMs that included either the M41L or L210W mutation showed reduced response to tenofovir.

###### Clinical efficacy

When tenofovir disoproxil fumarate and lamivudine were combined with efavirenz in treatment-naïve patients with HIV-1, the proportion of patients (ITT) with HIV-RNA <50 copies/ml were 76.3% and 67.9% at 48 and 144 weeks, respectively. No specific studies with the combination tenofovir disoproxil fumarate, emtricitabine and efavirenz have been conducted in adolescents.

###### 5.2 Pharmacokinetic properties

###### Efavirenz

###### Absorption and Bioavailability

Bioavailability is 40% to 45% without food. Food increases absorption significantly. Time to peak plasma concentrations (3 - 5 hours) did not change following multiple dosing and steady-state plasma concentrations were reached in 6 - 7 days.

Following single dose administration of one tablet of Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets in healthy volunteers, mean (±SD) efavirenz C<sub>max</sub> value was 2889 (±785) ng/ml and the corresponding value for AUC<sub>0-72</sub> was 64850 (±21728) ng·h/ml. The mean efavirenz t<sub>max</sub> value was 4.29 (±1.61) hours.

###### Distribution

Efavirenz is highly bound (more than 98%) to human plasma proteins, predominantly albumin. In HIV-1 infected adults (200 to 600 mg once daily for at least one month), mean cerebrospinal fluid concentrations (0.69% of the corresponding plasma concentration) were reached. This proportion is approximately 3-fold higher than the non-protein-bound (free) fraction of efavirenz in plasma.

###### Metabolism

Efavirenz is principally metabolized by the cytochrome P450 system to hydroxylated metabolites. These metabolites are essentially inactive against HIV-1. *In vivo* studies, supported by *in vivo* observations, suggest that CYP3A4 and CYP2B6 are the major isoenzymes responsible for efavirenz metabolism. Efavirenz has been shown to induce cytochrome P450 enzymes, resulting in the induction of its own metabolism.

###### Elimination

Efavirenz has a relatively long terminal half-life of 17 to 154 hours after single doses, and 40 - 55 hours after multiple doses. In individuals with certain mutant CYP2B6 genotypes (e.g. the T17 genotype at C616T) the terminal half-life may be substantially prolonged, and drug exposures higher. These genotypes are particularly common among Africans and African Americans. In patients with liver impairment, lower efavirenz clearance and higher drug exposures have been reported. Approximately 14 - 34% of a radio-labelled dose of efavirenz was recovered in the urine and less than 1% of the dose was excreted in urine as unchanged efavirenz.

###### Lamivudine

###### Absorption and Bioavailability

Lamivudine is rapidly absorbed following oral administration. Bioavailability is between 80 and 85%. Following single dose administration of one tablet of Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets in healthy volunteers, the mean (±SD) lamivudine C<sub>max</sub> value was 2452 (±706) ng/ml and the corresponding value for AUC was 13457 (±3717) ng·h/ml. The mean (±SD) lamivudine t<sub>max</sub> value was 1.92 (±0.93) hours.

Co-administration of lamivudine with food results in a delay of t<sub>max</sub> and a lower C (decreased by t<sub>max</sub> and a lower C<sub>max</sub> (decreased by 47%). However, the extent (based on the AUC) of lamivudine absorbed is not influenced.

###### Distribution

Intravenous studies with lamivudine showed that the mean apparent volume of distribution is 1.3 L/kg. Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited binding to the major plasma protein albumin (<36% serum albumin *in vitro*).

###### Metabolism

Metabolism of lamivudine is a minor route of elimination. Lamivudine is predominantly cleared unchanged by renal excretion. The likelihood of metabolic drug interactions with lamivudine is low due to the small extent of hepatic metabolism (5 - 10%) and low plasma protein binding.

###### Elimination

The observed lamivudine half-life of elimination is 5 to 7 hours. The half-life of intracellular lamivudine triphosphate has been estimated to approximately 22 hours. The mean systemic clearance of lamivudine is approximately 0.22 l/h/kg, with predominantly renal clearance (> 70%), including tubular secretion through the organic cationic transport system.

###### Special populations

**Renal impairment:** Studies in patients with renal impairment show that lamivudine elimination is affected by renal dysfunction. Dose reduction is recommended for patients with creatinine clearance ≤50 ml/min (see section 4.2).

###### Tenofovir disoproxil fumarate

Tenofovir disoproxil fumarate is a water-soluble ester prodrug, which is rapidly converted *in vivo* to tenofovir and formaldehyde. Tenofovir is converted intracellularly to tenofovir monophosphate and to the active component, tenofovir diphosphate.

###### Absorption

Following oral administration of tenofovir disoproxil fumarate to HIV infected patients, tenofovir disoproxil fumarate is rapidly absorbed and converted to tenofovir. The oral bioavailability of tenofovir from tenofovir disoproxil fumarate in fasted patients was approximately 25%.

Administration of tenofovir disoproxil fumarate with a high fat meal enhanced the oral bioavailability, with an increase in tenofovir AUC by approximately 40% and C<sub>max</sub> by approximately 14%.

Following single dose administration of one tablet of Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets in healthy volunteers, the mean (±SD) tenofovir C<sub>max</sub> value was 277 (±79) ng/ml and the corresponding value for AUC was 2358 (±627) ng·h/ml. The mean (±SD) tenofovir t<sub>max</sub> value was 1.17 (±0.57) hours.

###### Distribution

Following intravenous administration the steady-state volume of distribution of tenofovir was estimated to be approximately 800 ml/kg. *In vitro* protein binding of tenofovir to plasma or serum protein was less than 0.7 and 7.2%, respectively, over the tenofovir concentration range 0.01 to 25 µg/ml.

###### Elimination

Tenofovir is primarily excreted by the kidney, both by filtration and an active tubular transport system with approximately 70-80% of the dose excreted unchanged in urine following intravenous administration. Total clearance has been estimated to be approximately 250 ml/kg (approximately 350 ml/min). Renal clearance has been estimated to be approximately 160 ml/kg (approximately 210 ml/min), which is in excess of the glomerular filtration rate. This indicates that active tubular secretion is an important part of the elimination of tenofovir. Following oral administration the terminal half-life of tenofovir is approximately 12 to 18 hours.

Studies have established the pathway of active tubular secretion of tenofovir to be influx into proximal tubule cell by the human organic anion transporters (OAT) 1 and 2 and efflux into the urine by the multidrug resistant protein 4 (MRP 4). *In vitro* studies have determined that neither tenofovir disoproxil fumarate nor tenofovir are substrates for the CYP450 enzymes.

###### Age and gender

Limited data on the pharmacokinetics of tenofovir in women indicate no major gender effect. Tenofovir exposure achieved in adolescent patients receiving oral daily doses of tenofovir 300 mg was similar to exposures achieved in adults receiving once-daily doses of tenofovir 300 mg.

Pharmacokinetic studies have not been performed in children or in the elderly (over 65 years). Pharmacokinetics have not been specifically studied in different ethnic groups.

###### Renal impairment

Pharmacokinetic parameters of tenofovir were determined following administration of a single dose of tenofovir disoproxil fumarate 300 mg to 40 non-HIV, non-HIV infected patients with varying degrees of renal impairment defined according to baseline creatinine clearance (CrCl) (normal renal function when CrCl > 80 ml/min; mild with CrCl = 50-79 ml/min; moderate with CrCl = 30-49 ml/min and severe with CrCl = 10-29 ml/min) compared with patients with normal renal function. The mean (±SD) tenofovir exposure increased from 2,185 (12%) ng·h/ml in subjects with CrCl > 80 ml/min to respectively 3,064 (30%) ng·h/ml, 6,009 (42%) ng·h/ml and 15,365 (45%) ng·h/ml in patients with mild, moderate and severe renal impairment. The dosing recommendations in patients with renal impairment, with increased dosing interval, are expected to result in higher peak plasma concentrations and lower Cr<sub>min</sub> levels in patients with renal impairment compared with patients with normal renal function. The clinical implications of this are unknown.

In patients with end-stage renal disease (ESRD) (CrCl < 10 ml/min) requiring haemodialysis, between dialysis tenofovir concentrations substantially increased over 48 hours achieving a mean C<sub>max</sub> of 1,032 ng/ml and a mean AUC<sub>0-48h</sub> of 42,857 ng·h/ml. It is recommended that the dosing interval for tenofovir disoproxil fumarate 300 mg is modified in patients with creatinine clearance < 50 ml/min or in patients who already have ESRD and require dialysis (see section 4.2).

The pharmacokinetics of tenofovir in non-haemodialysis patients with creatinine clearance < 10 ml/min and in patients with ESRD managed by peritoneal or other forms of dialysis have not been studied.

###### Hepatic impairment

A single 300 mg dose of tenofovir disoproxil fumarate was administered to non-HIV, non-HIV infected patients with varying degrees of hepatic impairment defined according to Child-Pugh/Turcotte (CPT) classification. Tenofovir pharmacokinetic parameters were not substantially altered in subjects with hepatic impairment suggesting that no dose adjustment is required in these subjects. The mean (±SD) tenofovir C<sub>max</sub> and AUC<sub>0-72</sub> values were 223 (24.8%) ng/ml and 2,050 (50.8%) ng·h/ml, respectively, in normal subjects compared with 289 (46.0%) ng/ml and 2,31 (43.5%) ng·h/ml in subjects with moderate hepatic impairment, and 305 (24.8%) ng/ml and 2,740 (44.0%) ng·h/ml in subjects with severe hepatic impairment.

Intracellular pharmacokinetics: Tenofovir diphosphate has an intracellular half-life of 10 hours in activated and 50 hours in resting peripheral blood mononuclear cells (PBMCs).

###### 5.3 Preclinical