1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient(s) with known effect

Each film coated tablet contains 60.00 mg of Lactose monohydrate.
Each film coated tablet contains 1.9 mmol (43 mg) sodium.

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film coated tablets.

White coloured, 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 not 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 can be 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 indicated or where dose modification is necessary, separate preparations of tenofovir disoproxil fumarate, lamivudine and efavirenz are available. Please refer to the Summary of Product Characteristics for these medicinal products.

If Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets is co-administered with rifampicin, 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 related to efavirenz (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 reason for discontinuation.

4.3 Contraindications

Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets is contraindicated in patients with clinically significant hypersensitivity to tenofovir, lamivudine, 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 Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets should not be administered concomitantly with other cytidine analogues such as emtricitabine. (see section 4.5).

Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets should not be administered concomitantly with adefovir dipivoxil.

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 HBV- and/or HCV co-infection. Discontinuation is recommended if hepatoxicity 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 pre-existing 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 4 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, hypophosphataemia 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, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-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 (infrequently 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, this risk cannot be excluded. Lactic acidosis may occur after a few to several months of NRTI treatment. Patients with hyperlactataemia 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 hyperlactataemia 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 limb fat in patients with lipoatrophy. 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) and metabolic disorders (hyperlactataemia, hyperlipasaemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, 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 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. Therefore patients should remain under close clinical observation by physicians or health care providers experienced in the treatment of HIV infection.

Immune Reactivation Syndrom

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.

Osteonecrosis

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 combination 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 below).

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 a 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

Didanosine
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 via transport proteins hOAT 1, hOAT 3 or MRP 4 (e.g. cidofovir) 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, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2 (see section 4.4).

Given that tacrolimus 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 isoform CYP2B6, but also by CYP3A. Therefore, agents that alter the activity of CYP2B6 or CYP3A 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-glucuronosyl transferases, CYP3A4, CYP2C9 and CYP2C19. In the great majority of cases where efavirenz interacts *in vivo* with known CYP3A 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 once 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 "↔", thrice daily as t.i.d., twice daily as "b.i.d.", and once daily as "q.d.").

Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerningco-administration**
ANTI-INFECTIVES		
Antiretrovirals		
Nucleoside analogues		
Zidovudine **Stavudine** **Abacavir**	No interaction expected	
Abacavir / tenofovir		Abacavir and Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets should not be co-administered, as the additive effect of abacavir is expected to be limited or absent
Emtricitabine / lamivudine		Emtricitabine and Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets should not be coadministerad, due to the similarity between emtricitabine 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		
Nevirapine **Etravirine**		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 (1400/200 mg q.d.) / efavirenz	Amprenavir C_{min} ↓ 36% at steady state	Avoid concomitant use of Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets and once-daily fosamprenavir regimen.
Saquinavir HCG/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 AUC_{ss} ↓ 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.
Ritonavir (500 mg b.i.d) / efavirenz	Interaction studies have shown moderate increases in the AUC for both ritonavir and efavirenz.	Avoid concomitant use of Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets with full-dose ritonavir, due to low tolerability.
Nelfinavir (various doses) / efavirenz	Interaction studies have shown variable results, including a 20% increase in nelfinavir AUC and C_{min}, as well as a 25% decrease in AUC and 45% decrease in C_{min}.	Concomitant use with Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets is only recommended when it is possible to monitor the plasma concentration of nelfinavir.
Lopinavir/ritonavir soft capsules or **oral solution /** efavirenz **Lopinavir/ritonavir tablets** (400/100 mg b.i.d.) (500/125 mg b.i.d.) /efavirenz **Lopinavir/ritonavir** (400 mg/100 mg b.i.d.) /tenofovir	Substantial decrease in lopinavir exposure. Lopinavir C_{min} ↓ ≈ 40% Lopinavir concentrations Similar to lopinavir/ritonavir 400/100 mg twice daily without efavirenz Lopinavir/ritonavir No significant effect on lopinavir/ritonavir PK parameters.	Insufficient data are available to make a dosing recommendation for lopinavir/ritonavir when dosed with Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets. Co-administration of lopinavir/ritonavir and Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets is not recommended.

	Tenofovir AUC ↑ 32% C_{max} ↔ C_{min} ↑ 51%	
Atazanavir/ritonavir/tenofovir disoproxil fumarate (300 mg q.d./100 mg q.d./300 mg q.d.) **Atazanavir/ritonavir**/efavirenz (400 mg q.d./100 mg q.d./600 mg q.d., all administered with food) **Atazanavir/ritonavir**/efavirenz (400 mg q.d./200 mg q.d./600 mg q.d., all administered with food)	Atazanavir AUC ↓ 25% (↓ 42 to ↓ 3) C_{max} ↓ 28% (↓ 50 to ↑ 5) C_{min} ↓ 26% (↓ 46 to ↑ 10) Co-administration of atazanavir/ritonavir with tenofovir resulted in increased exposure to tenofovir. Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders. Atazanavir AUC ↔* (↓ 9% to ↑ 10%) C_{max} ↑ 17%* (↑ 8 to ↑ 27) C_{min} ↓ 42%* (↓ 31 to ↓ 51) Atazanavir AUC ↔*/** (↓ 10% to ↑ 26%) C_{max} ↔*/** (↓ 5% to ↑ 26%) C_{min} ↑ 12%*/** (↓ 16 to ↑ 49) (CYP3A4 induction). * When compared to atazanavir 300 mg/ritonavir 100 mg q.d. in the evening without efavirenz. This decrease in atazanavir C_{min} might negatively impact the efficacy of atazanavir. ** based on historical comparison. Co-administration of efavirenz with atazanavir/ritonavir is not recommended.	Co-administration of atazanavir/ritonavir and Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets is not recommended.
Tipranavir/ritonavir / efavirenz	Appropriate data on the interaction between the approved tipranavir regimen and efavirenz are lacking.	The combination of Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets and tipranavir/ritonavir should be avoided.

Darunavir/ritonavir (300/100 mg b.i.d) / efavirenz **Darunavir/ritonavir** (300 mg/100 mg b.i.d.) / tenofovir	Darunavir AUC at steady state ↓ 13%, C_{min} ↓ 31%. Efavirenz AUC ↑ 21%, C_{min} ↑ 17% Darunavir No significant effect on darunavir/ritonavir PK parameters. Tenofovir AUC ↑ 22% C_{min} ↑ 37%	The clinical significance of the changes in darunavir and efavirenz concentrations has not been established, and may vary depending on, e.g., whether there is clinically significant resistance to darunavir. Darunavir/ritonavir should be used with caution in combination with Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets.
CCR-5 antagonists		
Maraviroc (100 mg b.i.d) / efavirenz 600 mg q.d	Maraviroc AUC ↓ 45% C_{max} ↓ 51%	When co-treating with maraviroc and efavirenz in the absence of a boosted PI, the maraviroc dose should be increased to 600 mg twice daily. For other combinations, please refer to the SmPC for the medicinal product containing maraviroc.
Integrase strand transfer inhibitors		
Raltegravir (400 mg single dose) / efavirenz **Raltegravir** (400 mg b.i.d.) / tenofovir	Raltegravir AUC ↓ 36% AUC ↑ 49% C_{max} ↑ 64%	No dosage adjustment is necessary if Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets and raltegravir are co-administered.
Antifungals		
Ketoconazole (400 mg single dose; efavirenz 600 mg to steady state) / efavirenz	Ketoconazole AUC ↓ 72%	Consider alternative antifungal agent, or use therapeutic drug monitorng (TDM) if available.
Itraconazole (200 mg b.i.d) / efavirenz	Itraconazole AUC at steady state ↓ 39%, C_{min} ↓ 44%	Consider alternative antifungal agent, or use TDM if available.
Posaconazole (400 mg b.i.d./400 mg q.d.) / efavirenz	Posaconazole AUC ↓50% C_{max} ↓ 45%	Concomitant use of posaconazole and efavirenz should be avoided.
Fluconazole (200 mg q.d) / efavirenz	No significant interaction	
Voriconazole (200 b.i.d) / efavirenz (600mg)	No data available	Efavirenz and voriconazole at standard doses must not be coadministered.
Voriconazole (200 mg b.i.d.) / efavirenz 400 mg q.d)	Voriconazole AUC_{ss}: ↓ 77%;	The dose reduction for efavirenz with voriconazole at standard dose

	efavirenz AUC_{ss} ↑ 44%	leads to a significant alteration in the pharmacokinetics of both drugs and must thus not be used.
Voriconazole (400 mg b.i.d) / efavirenz 300 mg q.d)	Voriconazole AUC_{ss} ↓ 7%; efavirenz AUC_{ss}↑ 17%; both compared with standard doses of voriconazole and efavirenz (200 mg b.i.d and 600 mg q.d, respectively)	If coadministration is considered necessary, voriconazole should be dosed 400 mg b.i.d and efavirenz 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.).
Antibacterials/Antituberculotics		
Clarithromycin (500 mg b.i.d, multiple doses) / efavirenz	Clarithromycin AUC ↓ 39%; 14-OH-chlaritromycin 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_{min} ↓ 32%	When co-treating, a dose increase of efavirenz from 600 mg to 800 mg q.d. should be considered.
Rifabutin (300 mg q.d) / efavirenz	Rifabutin AUC_{ss} ↓ 38%	Increase rifabutin dose by 50% if co-treating with
Antimalarials		
Atovaquone **Chloroquine** **Mefloquine** **Proguanil,** **Sulfadoxine** **Pyrimethamine** / efavirenz	No formal interaction studies available. Drug interactions and safety in coadministration with efavirenz has not been systematically evaluated; on a theoretical basis, clinically significant drug interactions with efavirenz are unlikely	
Amodiaquine/artesunate (600/250 mg q.d.) / efavirenz	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 ↑ 114 and	Possibly increased hepatic toxicity. Avoid combination.

	302% respectively	
Quinine / efavirenz	No formal interaction study available Quinine is extensively metabolised by CYP3A. Coadministration with efavirenz may decrease quinine exposure, and reduce the antimalarial effect.	If possible, an alternative agent to quinine should be used in co-treatment with efavirenz
Lumefantrine, halofantrine / efavirenz	No formal interaction studies available. These agents are metabolised by CYP3A; hence, co-treatment with efavirenz may decrease exposure.	Co-treatment is not recommended.
Artemisinin and its derivatives / efavirenz	No formal interaction studies available Artemisinin and its derivatives are transformed into active metabolites by CYP3A. Exposure may be decreased by efavirenz. Empirical data are lacking and possible clinical consequences are unknown	
ANTIVIRALS AGAINST HBV		
Adefovir dipivoxil / tenofovir	AUC ↔ C_{max} ↔	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_{max} ↔	No clinically significant pharmacokinetic interactions when Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets is co-administered with entecavir.
ANTICONVULSANTS		
Carbamazepine (400 mg q.d) / efavirenz	Carbamazepine AUC_{ss} ↓ 27%, C_{min} ↓ 35%; efavirenz AUC_{ss} ↓ 36%, C_{min} ↓ 47%	Co-administration should be avoided unless plasma concentrations of carbamazepine and efavirenz can be monitored.
Phenytoin / 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.
Valproic acid (250 mg b.i.d) / efavirenz		No significant interaction is likely.
Vigabatrin	No significant interaction is likely	Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets and vigabatrin can be co-administered without dose adjustment.
CARDIOVASCULAR AGENTS		
Calcium channel blockers		
Diltiazem (240 mg q.d.) / efavirenz	Diltiazem AUC ↓ 69% Desacetyl diltiazem AUC ↓75% N-monodesmethyl diltiazem AUC ↓37%	Monitor the clinical effect of diltiazem and increase dose if necessary.
Verapamil, felodipine, nifedipine, nicardipine / efavirenz	Interaction not studied. Calcium channel blocker exposure is likely to be lowered in co-treatment with efavirenz.	Monitor clinical effect and increase calcium channel blocker dose if necessary.
LIPID LOWERING AGENTS		
Atorvastatin (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.
Pravastatin (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.
Simvastatin 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.
Rosuvastatin / efavirenz		Interaction not studied. Rosuvastatin is largely excreted unchanged via the faeces; therefore metabolic drug interaction with efavirenz is not expected.
HORMONAL CONTRACEPTIVES		
Ethinylestradiol/norgestimate (0.035 mg + 0.25 mg q.d) /	No change in ethinylestradiol exposure.	A reliable method of barrier contraception should be used in

efavirenz	Levonorgestrel AUC ↓ 83%, norelgestromin AUC ↓ 64% (active metabolites).	addition to oral contraceptives.
DMPA (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.
Etonogestrel (implant) / efavirenz	Interaction not studied. Decreased exposure of etonogestrel may be expected due to the CYP3A induction of efavirenz. There have been occasional postmarketing reports of contraceptive failure with etonogestrel in efavirenz-exposed patients	A reliable method of barrier contraception must be used in addition to hormonal contraception.
IMMUNOSUPPRESSANTS		
Tacrolimus, cyclosporine, sirolimus / efavirenz	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		
Methadone / efavirenz	Methadone AUC ↓ 52%	Monitor for withdrawal symptoms and increase methadone dose if necessary.
Buprenorphine / efavirenz	Buprenorphine AUC ↓ 50%; norbuprenorphine AUC ↓ 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.
Warfarin / efavirenz	No interaction study available Co-administration may decrease (and less likely increase warfarin	Monitor INR. Dose adjustments of warfarin may be necessary.

	exposure.	
Lorazepam (2mg single dose) / efavirenz	Lorazepam AUC ↑ 7% (↑ 1 to ↑ 14)	No dose adjustment necessary
Midazolam, Triazolam / efavirenz	No interaction study available	These benzodiazepines are metabolised by CYP3A. While efavirenz is an inducer of CYP3A in vivo, it acts as an inhibitor in vitro. The impact of co-administration on midazolam and triazolam pharmacokinetics is unknown. Co-administer with caution.
St. John's Wort *(hypericum perforatum)* / efavirenz	No interaction study available	Concomitant treatment contraindicated. Co-administration likely to decrease efavirenz levels and to precipitate virological 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.apregistry.com) 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.apregistry.com).

No increased risk of birth defects has been reported for lamivudine (www.apregistry.com). 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 and/or somnolence. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving and operating machinery.

4.8 Undesirable effects

The following adverse events have been reported in 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 (≥1/1000, <1/100), rare (≥1/10,000, <1/1000), 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: lipodystrophy, 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: dyspnea

Nervous system disorders
Very common: dizziness
Common: abnormal dreams, disturbance in attention, headache, insomnia, somnolence.
Unommon: 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

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
Unknown: 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
Unommon: gynaecomastia
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 reconstitution 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 87 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 600 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

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

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 δ) are not inhibited by efavirenz.

Lamivudine, the negative enantiomer of 2'-deoxy-3'-thiacytidine, is a dideoxynucleoside analogue. Tenofovir disoproxil fumarate is converted *in vivo* to tenofovir, a nucleoside monophosphate (nucleotide) analogue of adenosine 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, G190S/A/E and Y188L; a single one of these mutations is sufficient to cause high-grade resistance. The cross resistance between efavirenz and nevirapine or delavirdine is extensive; therefore patients who have experienced virological failure with either of these drugs, are likely to harbour virus not susceptible to efavirenz, and vice versa. With an accumulating number of NNRTI mutations, the susceptibility to etravirine 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 delavirdine 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 vitro 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 of antiretroviral agents. M184V confers full cross-resistance against emtricitabine. Zidovudine 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 mutant shows a <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 67.8% 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 of administration of one tablet of Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablets in healthy volunteers, mean (±SD) efavirenz C_{max} value was 2689 (±785) ng/ml and the corresponding value for AUC0-72h was 64850 (±21728) ng.h/ml. The mean efavirenz tmax value was 4.28 (±1.61) hours.

Distribution

Efavirenz is highly bound (more than 99%) to human plasma proteins, predominantly albumin. In HIV-1 infected patients who received efavirenz 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 metabolised by the cytochrome P450 system to hydroxylated metabolites. These metabolites are essentially inactive against HIV-1. In vitro 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 T/T genotype at G516T) 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_{max} value was 2483 (±706) ng/ml and the corresponding value for AUC was 13457 (±3717) ng.h/ml. The mean (±SD) lamivudine tmax value was 1.92 (±0.93) hours.

Co-administration of lamivudine with food results in a delay of t_{max} and a lower C_{max} (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 0.32 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_{max} 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_{max} value was 277 (±79) ng/ml and the corresponding value for AUC was 2358 (±627) ng.h/ml. The mean (±SD) tenofovir tmax 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 230 ml/h/kg (approximately 300 ml/min). Renal clearance has been estimated to be approximately 160 ml/h/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 (hOAT) 1 and 3 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-HBV 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 (%CV) 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 15,985 (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 C_{min} 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_{max} of 1,032 ng/ml and a mean AUC0-48h 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-HBV 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 (%CV) tenofovir C_{max} and AUC0-∞ values were 223 (34.8%) 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 safety data

Efavirenz

Preclinical data revealed no special hazard for humans other than those observed in clinical studies based on conventional studies of safety, pharmacology, repeated dose toxicity, and genotoxicity. In reproductive toxicology studies, 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. Carcinogenicity studies showed an increased incidence of hepatic and pulmonary tumours in female mice, but not in male mice.

Lamivudine

Administration of lamivudine in animal toxicity studies at high doses was not associated with any major organ toxicity. Lamivudine was not mutagenic in bacterial tests, but showed activity in an *in vitro* cytogenetic assay and the mouse lymphoma assay. Lamivudine was not genotoxic *in vitro* at doses that gave plasma concentrations around 40-50 times higher than the anticipated clinical plasma levels. As the *in vitro* mutagenic activity of lamivudine could not be confirmed in *in vivo* tests, it is concluded that lamivudine should not represent a genotoxic hazard to patients undergoing treatment.

The results of long-term carcinogenicity studies in rats and mice did not show any carcinogenic potential relevant for humans.

Tenofovir

Preclinical studies conducted in rats, dogs and monkeys revealed target organ effects in gastrointestinal tract, kidney, bone and a decrease in serum phosphate concentration. Bone toxicity was diagnosed as osteomalacia (monkeys) and reduced bone mineral density (rats and dogs). Findings in the rat and monkey studies indicated that there was a substance-related decrease in intestinal absorption of phosphate with potential secondary reduction in bone mineral density. However, no conclusion could be drawn on the mechanism(s) underlying these toxicities.

Reproductive studies were conducted in rats and rabbits. There were no effects on mating or fertility parameters or on any pregnancy or foetal parameter. There were no gross foetal alterations of soft or skeletal tissues. Tenofovir disoproxil fumarate reduced the viability index and weight of pups in peri-post natal toxicity studies.

Genotoxicity studies have shown that tenofovir disoproxil fumarate was negative in the *in vivo* mouse bone marrow micronucleus assay but was positive for inducing forward mutations in the *in vitro* L5178Y mouse lymphoma cell assay in the presence or absence of S9 metabolic activation. Tenofovir disoproxil fumarate was positive in the Ames test (strain TA 1535) in two out of three studies, once in the presence of S9 mix (6.2- to 6.8-fold increase) and once without S9 mix. Tenofovir disoproxil fumarate was also weakly positive in an *in vivo* / *in vitro* unscheduled DNA synthesis test in primary rat hepatocytes.
Tenofovir disoproxil fumarate did not show any carcinogenic potential in a long-term oral carcinogenicity study in rats. A long-term oral carcinogenicity study in mice showed a low incidence of duodenal tumours, considered likely related to high local concentrations of tenofovir disoproxil fumarate in the gastrointestinal tract at a dose of 600 mg/kg/day. While the mechanism of tumour formation is uncertain, the findings are unlikely to be of relevance to humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet

Croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium chloride and sodium lauryl sulphate.

Film coat

Polyethylene glycol , polyvinyl alcohol , talc and titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30°C. Store in the original container. Protect from light.

6.5 Nature and contents of container

Bottle of 30's.

6.6 Instructions for use and handling and disposal

No special requirements.

7. MARKETING AUTHORIZATION HOLDER

Mylan Laboratories Limited

REFERENCE

General reference sources for this SmPC include:

European SmPC, Sustiva, available at:
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000249/WC500058311.pdf

European SmPC, Viread, available at:
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000419/WC500051737.pdf
Viread, US prescribing information, available at: www.gilead.com/pdf/viread_pi.pdf

European SmPC, Epivir, available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000107/WC500027572.pdf

WHO: Antiretroviral therapy for HIV infection in adults and adolescents. Available at: http://whqlibdoc.who.int/publications/2010/9789241599764_eng.pdf

Further references relevant to sections of the SmPC include:

Section 4.5
van Leth et al Lancet. 2004;363:1253-63
European SmPC Telzir. Available at:
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000534/WC500035345.pdf
European SmPC Crixivan. Available at:
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000128/WC500035730.pdf
Smith et al. Antimicrob Agents Chemother, 2005, 49(8): 3558-3561
Kaletra, Scientific Discussion. Available at:
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000368/WC500039040.pdf
European SmPC Aptivus. Available at:
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000631/WC500025936.pdf
European SmPC Prezista. Available at:
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000707/WC500041756.pdf
Sriwiriyajan et al. Eur J Clin Pharmacol 2007;63:479-83
European SmPC Vfend: Available at:
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000387/WC500049756.pdf
German P, et al. 14th CROI, Los Angeles, February 2007, abstract 577
DiCenzo et al. Antimicrob Agents Chemother 2004; 48: 4328-4331
SE Cohn et al. Clin Pharm Ther 2007; 81:222-7
Clarke et al. Br J Clin Pharmacol 2001; 51:213–17.
Wire et al. AIDS 2004;18:897-907
Aarnoutse et al. Clin Pharmacol Ther 2002;71:57-67
European SmPC Invirase. Available at:
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000113/WC500035084.pdf
Reyataz, US prescribing information, available at: packageinserts.bms.com/pi/pi_reyataz.pdf

Section 4.6.
www.apregistry.com. Antiretroviral Pregnancy Registry. Available at :
WHO: Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: http://whqlibdoc.who.int/publications/2010/9789241599818_eng.pdf

Section 5.1
Gallant et al, JAMA 2004 ;292 :191-201
The Stanford HIV drug resistance database, available at: http://hivdb.stanford.edu

Section 5.2
Haas et al. AIDS 2004 ;18:2391-400
Klein et al. Pharmacogenet Genomics 2005;15:861-73
Barreiro et al. J Infect Dis 2007;195:973-9

Zambia Regn No.: 014/030
Zimbabwe Regn No.: 2012/7.13/4758

POM | **Schedule 2** | **PP** | **List - 1**

Manufactured by

Mylan Laboratories Limited
Plot No H-12 & H-13, MIDC, WALUJ,
Aurangabad - 431136
Maharashtra, INDIA.