SUMMARY OF PRODUCT CHARACTERISTIC

1. NAME OF THE MEDICINAL PRODUCT

Efavirenz/ Lamivudine/ Tenofovir Disoproxil Fumerate Tablet 400mg/300mg/300mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Efavirenz USP …….....400mg

Lamivudine USP…….....300mg

Tenofovir Disoproxil Fumarate 300mg

Equivalent to 245 mg of Tenofovir Disoproxil

<Excipient(s):>
For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL form

Film coated Tablet

4. Clinical Particulars

4.1 Therapeutic indications

Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 400mg/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.

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

4.2 Posology and method of administration

Adults and adolescents: the recommended dose of Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 400mg/300mg/300mg Tablets is one tablet taken orally once daily.

Method of administration

It is recommended that Efavirenz/Lamivudine/ Tenofovir Disoproxil Fumarate 400mg/300mg/300mg Tablets be swallowed whole with water.

It is recommended that Efavirenz/Lamivudine/ Tenofovir Disoproxil Fumarate 400mg/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.

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

Children

Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 400mg/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 400mg/300mg/300mg Tablets should be administered with caution to elderly patients.

Dose adjustments

Where discontinuation of therapy with one of the components of Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 400mg/300mg/300mg Tablets is indicated or where dose modification is necessary, separate preparations of tenofovir disoproxil fumarate, lamivudine and efavirenz are available.

If Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 400mg/300mg/300mg Tablets is co-administered with rifampicin, an additional 200 mg/day (800 mg total) of efavirenz may be considered.

Renal impairment

Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 400mg/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.

Hepatic impairment

If Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 400mg/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.

If therapy with Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 400mg/300mg/300mg Tablets is discontinued, consideration should be given to the long half-life of efavirenz and long intracellular half-lives of tenofovir and lamivudine. Because of inter-patient 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 400mg/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 400mg/300mg/300mg Tablets due to the risk of decreased plasma concentrations and reduced clinical effects of efavirenz.

Efavirenz significantly decreases voriconazole plasma concentrations while voriconazole also significantly increases efavirenz plasma concentrations. Since Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 400mg/300mg/300mg Tablets is a fixed-dose combination product, the dose of efavirenz cannot be altered; therefore, voriconazole and Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 400mg/300mg/300mg Tablets must not be co-administered.

4.4 Special warnings and precautions for use

General: As a fixed combination, Efavirenz/ Lamivudine/Tenofovir Disoproxil Fumarate 400mg/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 400mg/300mg/300mg Tablets should not be administered concomitantly with other cytidine analogues such as emtricitabine. Efavirenz/ Lamivudine/Tenofovir Disoproxil Fumarate 400mg/300mg/300mg Tablets should not be administered concomitantly with adefovir dipivoxil.

Transmission of HIV: Treatment with Efavirenz/ Lamivudine/Tenofovir Disoproxil Fumarate 400mg/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 400mg/300mg/300mg Tablets and didanosine is not recommended since exposure to didanosine is significantly increased following co-administration with tenofovir disoproxil fumarate.

Liver disease: Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 400mg/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. 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.

Lamivudine and tenofovir disoproxil fumarate are also active against HBV. Therefore, discontinuation of Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate

400mg/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 400mg/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 400mg/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.

Central nervous system and psychiatric effects: Central nervous system and psychiatric side effects are very common after starting efavirenz. 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 400mg/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 400mg/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.

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 400mg/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.

Consideration should also be given to interrupting treatment with Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 400mg/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 400mg/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: Decreases in bone mineral density of spine and changes in bone biomarkers may occur. Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 400mg/300mg/300mg Tablets should only be used in adolescents under the age of 18 if the benefits are considered to exceed the risk.

Bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy. 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.

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.

Pancreatitis: Treatment with Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 400mg/300mg/300mg Tablets should be stopped immediately if clinical signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur.

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 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.

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.

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 400mg/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.

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.

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.

The following list of interactions should not be considered exhaustive, but as representative of the classes of medicinal products where caution should be exercised.

Medicinal products by therapeutic areas	**Interaction**	**Medicinal products by therapeutic areas Recommendations concerning co**
ANTI-INFECTIVES		
Antiretrovirals		
Nucleoside analogues **Zidovudine, Stavudine, Abacavir**		
Abacavir / tenofovir		Abacavir and Efavirenz/Lamivudine/Tenofov ir Disoproxil Fumarate 400mg/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/Tenofov ir Disoproxil Fumarate 400mg/300mg/300mg Tablets should not be coadministerad, due to the similarity between emtricitabine and lamivudine, and consequently expected lack of additive effects
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 coadministration. 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. Coadministration of Efavirenz/Lamivudine/Tenofov ir Disoproxil Fumarate 400mg/300mg/300mg Tablets and didanosine is not recommended
Non-nucleoside inhibitors of reverse transcriptase **Nevirapine Etravirine**		Concomitant use with Efavirenz/Lamivudine/Tenofov ir Disoproxil Fumarate 400mg/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 Ctrough ↓ 17% No significant interaction with twice daily regimen at steady state	No dose adjustment necessary.
Fosamprenavir/ritonavir (1400/200 mg q.d.) / efavirenz	Amprenavir Cmin: ↓ 36% at steady state	Avoid concomitant use of Efavirenz/Lamivudine/Tenofov ir Disoproxil Fumarate

		400mg/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 400mg/300mg/300mg Tablets. Co-administration with saquinavir, with or without ritonavir, is not recommended.
Indinavir (800 mg t.i.d) / efavirenz	Indinavir AUCss ↓ 25%, Ctrough ↓ 50%	Concomitant use of Efavirenz/Lamivudine/Tenofov ir Disoproxil Fumarate 400mg/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/Tenofov ir Disoproxil Fumarate 400mg/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 Cmin, as well as a 25% decrease in AUC and 45% decrease in Cmin.	Concomitant use with Efavirenz/Lamivudine/Tenofov ir Disoproxil Fumarate 400mg/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 Cmin ↓ ≈ 40% Lopinavir concentrations: similar to lopinavir/ritonavir 400/100 mg twice daily without efavirenz Lopinavir/ritonavir: No significant effect on lopinavir/ritonavir PK parameters. Tenofovir: AUC: ↑ 32% Cmax: ↔ Cmin: ↑ 51%	Insufficient data are available to make a dosing recommendation for lopinavir/ritonavir when dosed with Efavirenz/Lamivudine/Tenofov ir Disoproxil Fumarate 400mg/300mg/300mg Tablets. Co-administration of lopinavir/ritonavir and Efavirenz/Lamivudine/Tenofov ir Disoproxil Fumarate 400mg/300mg/300mg Tablets is not recommended.
Atazanavir/ritonavir/t	Atazanavir:	Co-administration of

enofovir disoproxil fumarate (300 mg q.d./100 mg q.d./300 mg q.d.)	AUC: ↓ 25% (↓ 42 to ↓ 3) Cmax: ↓ 28% (↓ 50 to ↑ 5) Cmin: ↓ 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/ritonavir and Efavirenz/Lamivudine/Tenofov ir Disoproxil Fumarate 400mg/300mg/300mg Tablets is not recommended.
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: ↔ (↓ 9% to ↑ 10%) Cmax: ↑ 17% (↑ 8 to ↑ 27) Cmin: ↓ 42% (↓ 31 to ↓ 51) Atazanavir: AUC: ↔ (↓ 10% to ↑ 26%) Cmax: ↔(↓ 5% to ↑ 26%) Cmin: ↑ 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 Cmin might negatively impact the efficacy of atazanavir.based on historical comparison. Co-administration of efavirenz with atazanavir/ritonavir 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/Tenofov ir Disoproxil Fumarate 400mg/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%, Cmin ↓ 31%. Efavirenz AUC ↑ 21%, Cmin ↑ 17% Darunavir: No significant effect on darunavir/ritonavir PK parameters. Tenofovir: AUC: ↑ 22% Cmin: ↑ 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/Tenofov ir Disoproxil Fumarate 400mg/300mg/300mg Tablets .
CCR-5 antagonists		
Maraviroc (100 mg b.i.d) / efavirenz 600 mg q.d	Maraviroc AUC: ↓ 45% Maraviroc Cmax: ↓ 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% Raltegravir AUC ↑ 49% Raltegravir Cmax ↑ 64%	No dosage adjustment is necessary if Efavirenz/Lamivudine/Tenofov ir Disoproxil Fumarate 400mg/300mg/300mg Tablets and raltegravir are coadministered.
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%, Cmin ↓ 44%	Consider alternative antifungal agent, or use TDM if available.
Posaconazole (400 mg b.i.d./400 mg q.d.) / efavirenz	Posaconazole: AUC ↓50% Cmax ↓ 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 AUCss: ↓ 77%; efavirenz AUCss: ↑ 44%	The dose reduction for efavirenz with voriconazole at standard dose 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 AUCss ↓ 7%; efavirenz AUCss↑ 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/Tenofov ir Disoproxil Fumarate 400mg/300mg/300mg Tablets, alternative formulations of efavirenz, tenofovir and lamivudine should be used
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	No clinically significant	No dosage adjustment is

mg single dose) / efavirenz (400 mg once daily),	pharmacokinetic interaction	necessary for either medicinal product
Rifampicin (600 mg q.d, multiple doses)/ efavirenz	Efavirenz AUC ↓ 26%, Cmin ↓ 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 AUCss ↓ 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 302% respectively	Possibly increased hepatic toxicity. Avoid combination.
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 cotreatment 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: ↔ Cmax: ↔	Efavirenz/Lamivudine/Tenofov ir Disoproxil Fumarate 400mg/300mg/300mg Tablets

		should not be administered concurrently with adefovir dipivoxil due to an expected lack of additive effect
Entecavir (1 mg q.d.)	AUC: ↔ Cmax: ↔	No clinically significant pharmacokinetic interactions when Efavirenz/Lamivudine/Tenofov ir Disoproxil Fumarate 400mg/300mg/300mg Tablets is co-administered with entecavir.
ANTICONVULSANTS		
Carbamazepine (400 mg q.d) / efavirenz	Carbamazepine AUCss: ↓ 27%, Cmin ↓ 35%; efavirenz AUCss: ↓ 36%, Cmin ↓ 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/Tenofov ir Disoproxil Fumarate 400mg/300mg/300mg Tablets and vigabatrin can be coadministered 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 cotreatment 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) / efavirenz	No change in ethinylestradiol exposure. Levonorgestrel AUC ↓ 83%, norelgestromin AUC ↓ 64% (active metabolites)	A reliable method of barrier contraception should be used in 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 efavirenzexposed 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/Tenofov ir Disoproxil Fumarate 400mg/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 exposure.	Monitor INR. Dose adjustments of warfarin may be necessary
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. Coadministration likely to decrease efavirenz levels and to precipitate virological failure.

4.6 Pregnancy and lactation

Pregnancy

Studies of efavirenz in animals have shown reproductive toxicity, including marked teratogenic effects. Cases of neural tube defects in infants born to women with first trimester exposure have been reported, The postmarketing data available 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. 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.

No increased risk of birth defects has been reported for lamivudine. However, risks to the fetus cannot be ruled out.

Due to the possible teratogenic effects of efavirenz, Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 400mg/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.

Lactation

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.

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

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).

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: dyspnoea

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

Reproductive system and breast disorders:

Uncommon: 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

4.9 Overdose

If overdose occurs the patient must be monitored for evidence of toxicity, 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

Mechanism of Action:

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.

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 AUC_{0-72}h was 64850 (±21728) ng.h/ml. The mean efavirenz t_{max} 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 t_{max} 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.

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 t_{max} 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.

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

Lactose Monohydrate, Croscarmellose sodium, Poloxamer, Hydroxypropyl Cellulose, Sodium lauryl sulfate, magnesium stearate, Microctystalline cellulose, pregelantinized starch, hypromellose, titanium dioxide, triacetin, ferric oxide.

6.2 Incompatibilities

Not applicable

This medicinal product must not be mixed with other medicinal products except those mentioned in Section 6.6.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30°C, in dry place and protected from light.

Keep all medicines out of reach of children.

6.5 Nature and contents of container

30's/90's HDPE Container without carton
30/90 Tablets packed in HDPE container and child resistant closure with 2 X 3gm silica sachets packed along with leaflet.

30's HDPE Container with carton
30 Tablets packed in HDPE container and child resistant closure with 2 X 3gm silica sachets packed in a carton along with leaflet.

6.6 Special Precaution for disposal

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. <APPLICANT/SUPPLIER>

Macleods Pharmaceuticals Ltd.
304, Atlanta Arcade, Marol Church Road,
Andheri (East), Mumbai- 400 059,
India
Phone: +91-22-66762800
Fax: +91-22-2821 6599
E-mail: exports@macleodsphara.com

8. WHO PREQUALIFICATION REFERENCE NUMBER

9. DATE OF <PREQUALIFICATION>/<RENEWAL OF PREQUALIFICATION>

<{DD/MM/YYYY}><{DD month YYYY}>

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Reference list

https://extranet.who.int/prequal/sites/default/files/HA466part4v1_1.pdf