Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets 600 mg/300 mg/300 mg 20xxxxx

Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets 600 mg/300 mg/300 mg 20xxxxx

Rx only

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

POM | **Schedule 2** | **PP**

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains Efavirenz 600mg, lamivudine 300mg and tenofovir disoproxil fumarate 300 mg equivalent to 245 mg of tenofovir disoproxil.

Each tablet contains 50 mg of lactose anhydrous.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White color, capsule shaped, biconvex film coated tablets debossed with 'L65' on one side and plain on the other side.

4. Clinical particulars

4.1 Therapeutic indications

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are fixed dose combination of efavirenz, lamivudine and tenofovir disoproxil. It is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and adolescents (from 10 years of age and weighing ≥ 35 kg).

The choice of Efavirenz, lamivudine and tenofovir disoproxil fumarate 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.

4.2 Posology and method of administration

Posology

Pediatric population

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are not recommended for use in children below 10 years of age or weighing less than 35 kg since appropriate dose adjustments cannot be made with this combination tablet.

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

Adults and adolescents

The recommended dose of Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets is one tablet taken orally once daily.

It is important that the patient takes the medicine regularly as prescribed. Missing doses can increase the risk of resistance to Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets and reduce its effectiveness.

The patient should take a missed dose if it was due fewer than 12 hours ago. If more than 12 hours have passed since the dose was due, the patient should omit the missed dose and take the next scheduled dose at the usual time. The patient should not take a double dose.

If the patient **vomits** within 1 hour of taking Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, the patient should take an extra dose. If vomiting occurs more than an hour after taking the dose, the patient does not need to take an extra dose and can take the next dose as usual when it is due.

Dose adjustments and discontinuation of therapy

Where discontinuation of therapy with one of the components of Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets is indicated or where dose modification is necessary, separate preparations of efavirenz, lamivudine and tenofovir disoproxil are available. Please refer to the Summary of Product Characteristics for these medicinal products.

If therapy with Efavirenz, lamivudine and tenofovir disoproxil fumarate 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.

If Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are co-administered with rifampicin in patients weighing ≥ 50 kg, an additional 200 mg/day (800 mg total) of efavirenz may be considered (see section 4.4 and 4.5).

Special populations

Elderly: Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should be administered with caution to elderly patients (see section 4.4).

Renal impairment: Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are 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 that cannot be achieved with the combination tablet (see sections 4.4 and 5.2).

Hepatic impairment: Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are not recommended for patients with moderate or severe hepatic impairment because there are insufficient data to determine whether dose adjustment is necessary. Patients with mild liver disease (Child-Pugh-Turcotte(CPT). Class A) may be treated with the normal recommended dose. Because of the extensive cytochrome P450-mediated metabolism of efavirenz and limited clinical experience in patients with hepatic impairment, caution should be exercised in administering.

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets to these patients (see sections 4.4, 4.5 and 5.2).

Method of administration

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should be taken with water and swallowed whole. The tablets should be taken on an empty stomach (see sections 4.4, 4.8 and 5.2).

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should preferably be taken before bedtime, in order to improve the tolerability of efavirenz with respect to undesirable effects on the nervous system (see section 4.8).

4.3 Contraindications

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are contraindicated in patients with clinically significant hypersensitivity to efavirenz, lamivudine or tenofovir, or to any of the excipients contained in the formulation.

Co-administration with terfenadine, astemizole, cisapride, midazolam, triazolam, pimozide, bepridil, or ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine). Competition for cytochrome P450 (CYP) 3A4 by efavirenz could result in inhibition of metabolism and create the potential for serious and/or life-threatening adverse reactions (for example, cardiac arrhythmias, prolonged sedation or respiratory depression) (see section 4.5).

Voriconazole and Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets must not be co-administered, since efavirenz significantly decreases voriconazole plasma concentrations while voriconazole also significantly increases efavirenz plasma concentrations (see section 4.5). No dose adjustment of efavirenz is possible with the fixed-dose combination product (see section 4.5).

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets and dasabuvir + ombitasvir/paritaprevir/ritonavir should not be co-administered. Concomitant use can result in ALT elevations and is expected to reduce the therapeutic effect of dasabuvir + ombitasvir/paritaprevir/ritonavir(see section 4.5).

Herbal preparations containing St.John's wort (*Hypericum perforatum*) must not be used while taking due to the risk of decreased plasma concentrations and reduced clinical effects of efavirenz (see section 4.5).

4.4 Special warnings and precautions for use

Concomitant use of other medicinal products:

As a fixed combination, Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should not be administered concomitantly with other medicinal products containing any of the same active components, efavirenz, lamivudine or tenofovir disoproxil. Co-administration with efavirenz may only be considered if needed for dose adjustment e.g. with rifampicin in patients weighing ≥ 50 kg (see section 4.2 and 4.5).

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should not be administered concomitantly with adefovir dipivoxil.

Co-administration of Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets and didanosine is not recommended since exposure to didanosine is significantly increased following co-administration with tenofovir disoproxil (see section 4.5). Rarely, pancreatitis and lactic acidosis, sometimes fatal have been reported.

No data are available on the safety and efficacy of combined efavirenz, lamivudine and tenofovir disoproxil in combination with other antiretroviral agents.

Concomitant use of Ginkgo biloba extracts is not recommended (see section 4.5).

Switching from a PI-based antiretroviral regimen

Currently available data indicate a trend that in patients on a PI-based antiretroviral regimen the switch to Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets may lead to a reduction of the response to the therapy (see section 5.1). These patients should be carefully monitored for rises in viral load and, since the safety profile of efavirenz differs from that of protease inhibitors, for adverse reactions.

Liver function:

Monitoring of liver enzymes before and during treatment is recommended for patients with underlying hepatic disease, including hepatitis B or C infection; patients with marked transaminase elevations; and patients treated with other medications associated with liver toxicity (see sections 4.2 and 4.8).

Hepatic failure has occurred in patients with no preexisting hepatic disease or other identifiable risk factors (see section 4.8). Therefore, liver enzyme monitoring should be also considered for patients without pre-existing hepatic dysfunction or other risk factors. In patients with persistent elevations of serum transaminases to greater than five times the upper limit of the normal range, the benefit of continued therapy with Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets needs to be weighed against the unknown risks of significant liver toxicity.

Patients with pre-existing liver dysfunction, or using other medicinal products associated with liver toxicity, have an increased frequency of liver function abnormalities during combination antiretroviral therapy (CART) and should be monitored according to standard practice. If there is clinical evidence of worsening liver disease or persistent elevations of serum transaminases in the range of 5 to 10 times the upper limit of normal, interruption or discontinuation of treatment with Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should be considered (see section 4.8). The benefit of continued therapy needs to be weighed against the potential risks of significant liver toxicity. Discontinuation is recommended if hepatotoxicity is symptomatic, or if the transaminase levels are > 10 times the upper limit of normal.

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

Physicians should refer to current relevant treatment guidelines for the optimal management of HIV infection in patients co-infected with HBV or HCV.

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.

Increased transaminase levels may occur months after starting efavirenz and may be more frequent in patients with HBV-and/or HCV co-infection.

Lamivudine and tenofovir disoproxil are also active against HBV. Therefore, discontinuation of Efavirenz, lamivudine and tenofovir disoproxil fumarate 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 therapy must be closely monitored with both clinical and laboratory follow-up for at least four months after stopping treatment. If appropriate, resumption of specific anti-hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, specific anti-hepatitis B therapy has to be resumed without interruption.

Psychiatric symptoms

Psychiatric adverse reactions have been reported in patients treated with efavirenz. Patients with a prior history of psychiatric disorders appear to be at greater risk of serious psychiatric adverse reactions. In particular, severe depression was more common in those with a history of depression. There have also been post-marketing reports of severe depression, death by suicide, delusions and psychosis-like behavior. Patients should be advised that if they experience symptoms such as severe depression, psychosis or suicidal ideation, they should contact their doctor immediately to assess the possibility that the symptoms may be related to the use of efavirenz, and if so, to determine whether the risk of continued therapy outweighs the benefits (see section 4.8).

Nervous system symptoms

Symptoms including, but not limited to, dizziness, insomnia, somnolence, impaired concentration and abnormal dreaming are frequently reported undesirable effects in patients receiving efavirenz 600 mg daily in clinical studies. Dizziness was also seen in clinical studies with lamivudine and tenofovir disoproxil. Headache has been reported in clinical studies with lamivudine (see section 4.8). Nervous system symptoms associated with efavirenz usually begin during the first one or two days of therapy and generally resolve after the first two to four weeks. Patients should be informed that if they do occur, these common symptoms are likely to improve with continued therapy and are not predictive of subsequent onset of any of the less frequent psychiatric symptoms.

Seizures

Convulsions have been observed in patients receiving efavirenz, generally in the presence of a known medical history of seizures. Patients who are receiving concomitant anticonvulsant medicinal products primarily metabolized by the liver, such as phenytoin, carbamazepine and phenobarbital, may required periodic monitoring of plasma levels. In a drug interaction study, carbamazepine plasma concentrations were decreased when carbamazepine was co-administered with efavirenz (see section 4.5). Caution must be taken in any patient with a history of seizures.

Rash

Mild-to-moderate rash has been reported with the individual components of Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. The rash associated with the efavirenz component usually resolves with continued therapy. Appropriate antihistamines and/or corticosteroids may improve tolerability and hasten the resolution of rash.

Severe rash associated with blistering, moist desquamation or ulceration has been reported in less than 1% of patients treated with efavirenz (see section 4.8). The incidence of erythema multiforme or Stevens-Johnson syndrome was approximately 0.1%. Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600 mg/300 mg /300 mg Tablets must be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. Experience with efavirenz in patients who discontinued other NNRTIs for rash is limited. Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets is not recommended for patients who have had a life-threatening cutaneous reaction (e.g., Stevens-Johnson syndrome) while taking an NNRTI.

Renal function:

Lamivudine and tenofovir disoproxil are primarily excreted by the kidneys, through a combination of glomerular filtration and active tubular secretion. Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets is not recommended for patients with moderate or severe renal impairment (creatinine clearance < 50 ml/min). Patients with moderate or severe renal impairment require a dose adjustment of lamivudine and tenofovir disoproxil that 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 in clinical practice (see section 4.8).

It is recommended that creatinine clearance/estimated glomerular function is calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. If the creatinine test is routinely available, use the estimated glomerular filtration rate at baseline before initiating TDF regimens. If the creatinine test is not routinely available urine dipsticks may be used to detect glycosuria or severe TDF nephrotoxicity in individuals without risk factors. Creatinine testing is particularly advisable for high-risk patients (those who are older or have underlying renal disease, long-term diabetes or uncontrolled hypertension concomitant with boosted PIs or nephrotoxic drugs) to detect and limit further progression of renal impairment. Benefit and risks should be carefully weighed. If available, also serum phosphate should be measured in these patients. If serum phosphate is < 1.5 mg/dl (0.48 mmol/l) or creatinine clearance is decreased to < 50 ml/min in any patient receiving this medicine renal function must be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations (see section 4.8, proximal tubulopathy). Since Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are a combination product and the dosing interval of the individual components cannot be altered, treatment with this medicine must be interrupted in patients with confirmed creatinine clearance < 50 ml/min or decreases in serum phosphate to < 1.0 mg/dl (0.32 mmol/l).

Interrupting treatment should also be considered in case of progressive decline of renal function when no other cause has been identified. Where discontinuation of therapy with one of the components is indicated or where dose modification is necessary, separate preparations of efavirenz, lamivudine and tenofovir disoproxil are available.

This medicine should be avoided with concurrent or recent use of a nephrotoxic medicinal product (e.g. high-dose or multiple non-steroidal anti-inflammatory drugs, aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir, interleukin-2). If concomitant use of Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600 mg/300 mg /300 mg Tablets and nephrotoxic agents is unavoidable, renal function must be monitored weekly (see section 4.5).

Elderly patients

Elderly patients are more likely to have decreased renal function; therefore caution should be exercised when treating elderly patients with tenofovir disoproxil.

Bone effects

In a controlled clinical study in adult patients 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 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 the 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.

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.

Renal and bone effects in adolescent population:

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.

There are uncertainties associated with the long-term effects of bone and renal toxicity. Moreover, the reversibility of renal toxicity cannot be fully ascertained. Therefore, a multidisciplinary approach is recommended to adequately weigh on a case by case basis the benefit/risk balance of treatment, decide the appropriate monitoring during treatment (including decision for treatment withdrawal) and consider the need for supplementation.

If renal abnormalities are suspected or detected during therapy with tenofovir disoproxil-containing treatment, then consultation with a nephrologist should be obtained to consider interruption of treatment. Interrupting treatment should be considered in case of progressive decline of renal function when no other cause has been identified.

The effects of tenofovir disoproxil-associated changes in BMD on long-term bone health and future fracture risk are currently unknown.

If bone abnormalities are detected or suspected in paediatric patients, consultation with an endocrinologist and/or nephrologist should be obtained.

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

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

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 HIVnegative 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.

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, *Pneumocystiis jirovecii* pneumonia) may arise and cause serious clinical conditions or aggravation of symptoms.

Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.8). Treatment should be instituted when necessary.

Effect of food

The administration of Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets with food may increase efavirenz exposure (see section 5.2) and may lead to an increase in frequency of adverse reactions (see section 4.8). It is recommended that Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets to be taken on an empty stomach, preferably at bedtime.

General

Transmission of HIV: while effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

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 a health care providers experienced in the treatment of HIV infection.

Important information about some of the other ingredients of Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets contains lactose. Patients with rare hereditary problems of galactose intolerance (e.g. galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption) may experience symptoms of intolerance when using it.

4.5 Interaction with other medicinal products and other forms of interaction

No drug interaction studies have been performed using Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. As this medicine contains efavirenz, lamivudine and tenofovir disoproxil, any interactions that have been identified with these agents individually may occur with this combination tablet. Interaction studies with these agents have only been performed in adults.

Contraindications of concomitant use

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets must not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, triazolam, pimozide, bepridil, or ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine), since inhibition of their metabolism may lead to serious, life-threatening events (see section 4.3).

Voriconazole

Co-administration of standard doses of efavirenz and voriconazole is contraindicated. Since Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets is a fixed-dose combination product, the dose of efavirenz cannot be altered; therefore, voriconazole and Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets must not be co-administered (see section 4.3 and Table 1).

Dasabuvir + ombitasvir/paritaprevir/ritonavir

Concomitant use of dasabuvir + ombitasvir/paritaprevir/ritonavir with Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are contraindicated, as this can result in ALT elevations, possibly due to enzyme induction by efavirenz. In addition, concomitant use is expected to decrease plasma concentrations of dasabuvir + ombitasvir/paritaprevir/ritonavir and reduce their therapeutic effect (see section 4.3 and Table 1).

St. John's wort (Hypericum perforatum)

Co-administration of Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets and St. John's wort or herbal preparations containing St. John's wort is contraindicated. Plasma levels of efavirenz can be reduced by concomitant use of St. John's wort due to induction of drug metabolizing enzymes and/or transport proteins by St. John's wort. If a patient is already taking St. John's wort, stop St. John's wort, check viral levels and if possible efavirenz levels. Efavirenz levels may increase on stopping St. John's wort. The inducing effect of St. John's wort may persist for at least 2 weeks after cessation of treatment (see section 4.3).

Concomitant use not recommended

As a fixed combination, Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should not be administered concomitantly with other medicinal products containing the components, lamivudine or tenofovir disoproxil. Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should not be co-administered with products containing efavirenz unless needed for dose adjustment e.g. with rifampicin (see section 4.2).

Due to similarities with lamivudine, this product should not be administered concomitantly with other cytidine analogues, such as emtricitabine.

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should not be administered concomitantly with adefovir dipivoxil.

Efavirenz is an *in vivo* inducer of CYP3A4, CYP2B6 and UGT1A1. Compounds that are substrates of these enzymes may have decreased plasma concentrations when co-administered with efavirenz. Efavirenz may be an inducer of CYP2C19 and CYP2C9; however, inhibition has also been observed *in vitro* and the net effect of co-administration with substrates of these enzymes is not clear (see section 5.2).

Efavirenz exposure may be increased when given with medicinal products (for example ritonavir) or food (for example, grapefruit juice) which inhibit CYP3A4 or CYP2B6 activity. Compounds or herbal preparations (for example Ginkgo biloba extracts and St. John's wort) which induce these enzymes may give rise to decreased plasma concentrations of efavirenz. Concomitant use of St. John's wort is contraindicated (see section 4.3). Concomitant use of Ginkgo biloba extracts is not recommended (see section 4.4).

In vitro and clinical pharmacokinetic interaction studies have shown that the potential for CYP- mediated interactions involving lamivudine and tenofovir disoproxil with other medicinal products is low.

Trimethoprim/sulfamethoxazole

Administration of trimethoprim/sulfamethoxazole 160 mg/800 mg results in a 40 % increase in lamivudine exposure, because of the trimethoprim component; the sulfamethoxazole component did not interact. However, unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary (see section 4.2). Lamivudine has no effect on the pharmacokinetics of trimethoprim on sulfamethoxazole. When concomitant administration is warranted, patients should be monitored clinically. Co-administration of lamivudine with high doses of co-trimoxazole for the treatment of Pneumocystis jirovecii pneumonia (PCP) and toxoplasmosis should be avoided.

Atazanavir/ritonavir

Insufficient data are available to make a dosing recommendation for atazanavir/ritonavir in combination with Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. Therefore co-administration of atazanavir/ritonavir and Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are not recommended (see Table 1).

Didanosine

Co-administration of Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets and didanosine is not recommended (see section 4.4 and Table 1).

Posaconazole

Concomitant use of posaconazole and Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should be avoided, as this decreases posaconazole plasma concentrations.

Renally eliminated medicinal products

Since lamivudine and tenofovir are primarily eliminated by the kidneys, co-administration of Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets with medicinal products that reduce renal function or compete for active tubular secretion (e.g. cidofovir) may increase serum concentrations of lamivudine, tenofovir and/or the co-administered medicinal products.

Use of Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should be avoided with concurrent or recent use of a nephrotoxic medicinal product. Some examples include, but are not limited to, aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2 (see section 4.4).

Cannabinoid test interaction

Efavirenz does not bind to cannabinoid receptors. False-positive urine cannabinoid test results have been reported with some screening assays in uninfected and HIV-infected subjects receiving efavirenz.Confirmatory testing by a more specific method such as gas chromatography/mass spectrometry is recommended in such cases.

Other interactions

Table 1: Interactions between the individual components of Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets and other medicinal products

(increase is indicated as "↑", decrease as "↓", no change as "↔", twice daily as "b.i.d.", once daily as "q.d." and once every 8 hours as "q8h")

Medicinal products by therapeutic areas	Interaction	Recommendationsconcerning coadministration
ANTI-INFECTIVES		
Antiretrovirals In general, this product is intended to be a complete antiretroviral regimen. Nonetheless, drug-drug interactions with antiretrovirals are listed below to allow full access to all relevant information		
Nucleoside analogues		
Zidovudine Stavudine Abacavir	No interaction expected	
Emtricitabine /lamivudine		Emtricitabine and Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should not be co-administered, 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 and tenofovir disoproxil fumarate tablets and didanosine is not recommended (see section 4.4).
Non-nucleoside inhibitors of reverse transcriptase		
Nevirapine Etravirine		Concomitant use 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 Cmax ↑ 17% No significant interaction with twice daily regimen at steady state.Amprenavir	No dose adjustment necessary
Fosamprenavir/ritonavir (1400/200 mg q.d.) / efavirenz	Cmin ↓ 36% at steady state	Avoid concomitant use of Efavirenz, lamivudine and tenofovir disoproxil fumarate 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 and tenofovir disoproxil fumarate tablets. Coadministration with saquinavir, with or without ritonavir, is not recommended.
Indinavir (800 mg t.i.d) / Efavirenz (200 mg q.d)	Indinavir AUC ↓ 31%, Ctrough ↓40%	Concomitant use with unboosted indinavir is not recommended.
Indinavir/ritonavir (800/100 mg b.i.d.) / efavirenz	Indinavir AUCss ↓25% Ctrough ↓ 50%	Concomitant use with boosted indinavir is only recommended when it is possible to monitor the plasma concentration of indinavir.
Ritonavir (500 mg b.i.d) / Efavirenz (600 mg q.d)	Interaction studies have shown moderate increases in the AUC for both ritonavir and efavirenz	Avoid concomitant use with full -dose ritonavir, due to low tolerability.
Lopinavir/ritonavir soft capsules or oral solution / Efavirenz Lopinavir/ritonavir tablets (400/100 mg b.i.d.)/efavirenz (600 mg q.d) (500/125 mg b.i.d.)/efavirenz (600 mg q.d) Lopinavir/ritonavir (400mg/100mgb.i.d.)/Tenofovir disoproxil (245 mg q.d)	Substantial decrease in lopinavir exposure Lopinavir Cmin ↓ 40% Lopinavir concentrations: similar to lopinavir/ritonavir 400/100 mg twice daily withoutEfavirenz Lopinavir/ritonavir: No significant effect on lopinavir/ritonavir PK parametersTenofovir: AUC: ↑ 32% Cmax: ↔ Cmin: ↑ 51%	Insufficient data are available to make a dosing recommendation for lopinavir/ritonavir when dosed with Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. Co-administration of lopinavir/ritonavir and Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets is not recommended.
Atazanavir 400mg / Efavirenz Atazanavir(400mgq.d.)/tenofovir	Atazanavir AUCss: ↓ 74% Cmin: ↓ 93% Atazanavir: AUC: ↓ 25% Cmax: ↓ 21% Cmin: ↓ 40% Tenofovir: AUC: ↑ 24% Cmax: ↑ 14% Cmin: ↑ 22%	Concomitant use of Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets and unboosted atazanavir is not recommended
Atazanavir/ritonavir/Tenofovir disoproxil (300 mg q.d./100 mg q.d./245 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% Cmax: ↓ 28% Cmin: ↓ 26% 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: ↔* Cmax: ↑ 17%* Cmin: ↓ 42%* Atazanavir: AUC: ↔*/** Cmax: ↔*/** Cmin: ↑ 12%*/** (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	Co-administration of atazanavir/ritonavir and Efavirenz, lamivudine and tenofovir disoproxil fumarate 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 and tenofovir disoproxil fumarate tablets and tipranavir/ritonavir should be avoided
Darunavir/ritonavir (300/100 mg b.i.d) / efavirenz (600 mg q.d) Darunavir/ritonavir (300 mg/100 mg b.i.d.) / tenofovir disoproxil (245 mg q.d)	Darunavir AUCss ↓ 13% Cmax ↓ 15% Cmin ↓ 31%. (CYP3A4 induction) Efavirenz AUC ↑ 21% Cmax ↑ 15% Cmin ↑17% (CYP3A4 induction) Darunavir: No significant effect On darunavir/ritonavir PK parameters. Tenofovir: AUC: ↑ 22% Cmin: ↑ 37%	Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets in combination with darunavir/ritonavir 800/100mg once daily may result in suboptimal darunavir Cmin.. If Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets is to be used in combination with darunavir/ritonavir, the darunavir/ritonavir 600/100mg twice daily regimen should be used. Darunavir/ritonavir should be used with cauti on in combination with Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets (see ritonavir). Monitoring of renal function may be indicated, particularly in patients with underlying systemic or renal disease, or in patients taking nephrotoxic agents
CCR-5 antagonists		
Maraviroc (100 mg b.i.d) / Efavirenz 600 mg q.d Maraviroc (300 mg b.i.d) / tenofovir 300 mg q.d	Maraviroc AUC: ↓45% Cmax: ↓ 51% Maraviroc AUC12h: ↔ Cmax: ↔ Tenofovir concentrations not measured, no effect is expected.	Refer to the SmPC for the medicinal product containing maraviroc.
Integrase strand transfer inhibitors		
Raltegravir (400 mg single dose) efavirenz	Raltegravir AUC ↓ 36% Cmax: ↓ 36% (UGT1A1 induction)	Efavirenz, lamivudine and tenofovir disoproxil fumarate tab lets and raltegravir can be co-administered without dose adjustment.
Raltegravir (400 mg b.i.d.) / tenofovir	Raltegravir AUC ↑ 49% Cmax ↑ 64% Tenofovir AUC: ↓ 10% Cmax: ↓ 23%	
ANTIVIRALS AGAINST HBV		
Adefovir dipivoxil / tenofovir	AUC: ↔ Cmax: ↔	Efavirenz, lamivudine and tenofovir disoproxil fumarate 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: ↔ Cmax: ↔	No clinically significant pharmacokinetic interactions when Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets is co-administered with entecavir.
ANTIVIRALS AGAINST HCV		
Boceprevir (800 mg 3 times daily) /Efavirenz (600 mg q.d.)	Boceprevir: AUC(0-8h): ↔19%* Cmax:↔ 8% Cmin:↓ 44% Efavirenz: AUC:↔ 20% Cmax:↔ 11% (CYP3A induction - effect on boceprevir) *0-8 hours No effect (↔) equals a decrease in mean ratio estimate of ≤20% or increase in mean ratio estimate of ≤25%	Plasma trough concentrations of boceprevir were decreased when administered with efavirenz. The clinical outcome of this observed reduction of boceprevir trough concentrations has not been directly assessed.
Telaprevir(1,125mg q8h)/Efavirenz (600 mg q.d.)	Telaprevir (relative to 750 mg q8h): AUC: ↓18% Cmax: ↓14% Cmin: ↓25% Efavirenz: AUC: ↓18% Cmax: ↓24% Cmin: ↓10% (CYP3A induction by efavirenz)	If when Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets and telaprevir are co -administered, telaprevir 1,125 mg every 8 hours should be used.
Simeprevir/Efavirenz (150 mg q.d./600 mg q.d.)	Simeprevir: AUC: ↓ 71% Cmax: ↓ 51% Cmin: ↓ 91%	Concomitant administration of simeprevir with efavirenz, resulted in significantly decreased plasma concentrations of simeprevir due to CYP3A induction by efavirenz, which may result in loss of therapeutic effect of simeprevir. Co -administration of simeprevir with Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets is not recommended.
Daclatasvir (60 mg q.d./120 mg q.d.) / Efavirenz 600 mg q.d.	↓ Daclatasvir AUC*: 0.68 Cmax*: 0.83 Cmin*: 0.41 Induction of CYP3A4 by efavirenz *results are dose normalised to 60 mg dose.	The dose of daclatasvir should be increased to 90 mg once daily when coadministered with Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets.
Dasabuvir + ombitasvir/paritaprevir/ritonavir /Efavirenz/emtricitabine/tenofovir disoproxil 600/300/245 mg q.d.	Co-administration of efavirenz (enzyme inducer) based regimens with paritaprevir /ritonavir + dasabuvir resulted in ALT elevations, possible by enzyme induction by efavirenz.	Concomitant use of dasabuvir + ombitasvir/paritaprevir/ritonavir with Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets.is contraindicated.
Sofosbuvir / Efavirenz (600 mg q.d.) Sofosbuvir / Tenofovir disoproxil (245 mg q.d.)	No clinically significant pharmacokinetic interaction No clinically significant pharmacokinetic interaction	No dose adjustment required for either medicinal product
ledipasvir (90 mg once daily) / sofosbuvir (400 mg once daily) / Efavirenz/emtricitabine/ tenofovir disoproxil (600 mg/ 200 mg/ 245 mg/ once daily) ledipasvir (90 mg once daily) / sofosbuvir (400 mg once daily) / Abacavir/ lamivudine (600 mg/ 300 mg once daily)	No clinically significant pharmacokinetic interaction No clinically significant pharmacokinetic interaction	No dose adjustment required for either medicinal product.
ANTIMYCOBACTERIALS AND ANTIBIOTICS		
Clarithromycin (500 mg b.i.d, multiple doses) / efavirenz	Clarithromycin AUC ↓ 39% Cmax ↓26% 14-OH chlaritromycin AUC ↑ 34% Cmax ↑49% Efavirenz AUC ↔ Cmax ↑ 11%	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%, Cmax ↓20% Cmin ↓ 32%	When co-treating, a dose increase of Efavirenz from 600 mg to 800 mg q.d. should be considered in patients weighing 50 kg or more. Individual tolerability and virological response should be considered when making the dose adjustment. No dose adjustment of rifampicin is recommended when given with Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets.
Rifabutin (300 mg q.d) / efavirenz	Rifabutin AUC ↓ 38% Cmax ↓32% Cmin ↓ 45%	Increase rifabutin dose by 50% if co-treating with Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets.
ANTIFUNGALS		
Fluconazole (200 mg q.d.) / efavirenz (400 mg q.d.)	No clinically significant interaction	No dose adjustment is necessary for either medicinal product.
Itraconazole (200 mg b.i.d) / efavirenz (600 mg q.d.)	Itraconazole AUCss ↓ 39%, Cmax ↓37% Cmin ↓ 44% Hydroxyitraconazole AUC ↓ 37%, Cmax ↓35% Cmin ↓ 43%	Consider alternative antifungal agent, or use TDM if available.
Posaconazole (400 mg b.i.d.) / efavirenz (400 mg q.d.)	Posaconazole: AUC ↓50% Cmax ↓ 45%	Concomitant use of posaconazole and Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets.should be avoided.
Voriconazole (200 mg b.i.d) / efavirenz (400 mg q.d)	Voriconazole: AUC: ↓ 77% Cmax: ↓ 61% Efavirenz: AUC: ↑ 44% Cmax: ↑ 38% (competitive inhibition of oxidative metabolism)	Co-administration of Efavirenz and voriconazole at standard doses is contraindicated (see section 4.3). As dose reduction of efavirenz cannot be accommodated for with Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, these m ust not be co -administered with voriconazole.
ANTIMALARIALS		
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. Coadministration of amodiaquine and Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should be avoided
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, lamivudine and tenofovir disoproxil fumarate tablets.
Lumefantrine Halofantrine / efavirenz	No formal interaction studies available. These agents are metabolised by CYP3A; hence, cotreatment With efavirenz may decrease exposure	Co-treatment with Efavirenz, lamivudine and tenofovir disoprox il fumarate tablets.may decrease antimal arial efficacy. When cotreating caution is recommended.
Artemether/Lumefantrine/Efavirenz (20/120 mg tablet, 6 doses of 4 tablets each over 3 days/600 mg q.d.)	Artemether: AUC: ↓ 51% Cmax: ↓ 21% Dihydroartemisinin (active metabolite): AUC: ↓ 46% Cmax: ↓ 38% Lumefantrine: AUC: ↓ 21% Cmax: ↔ Efavirenz: AUC: ↓ 17% Cmax: ↔ (CYP3A4 induction)	Co-treatment with Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets may decrease antimalarial efficacy. When cotreating caution is 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.	
Atovaquone and proguanil Hydrochloride (250/100 mg single dose)/Efavirenz (600 mg q.d.)	Atovaquone: AUC: ↓ 75% Cmax: ↓44% Proguanil: AUC: ↓43% Cmax: ↔	Concomitant administration of atovaquone/proguanil with Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should be avoided whenever possible.
ANTICONVULSANTS		
Carbamazepine (400 mg q.d) / efavirenz (600 mg q.d.)	Carbamazepine: AUC: ↓ 27% Cmax: ↓ 20% Cmin: ↓ 35% Efavirenz: AUC: ↓ 36% Cmax: ↓ 21% Cmin: ↓ 47% (decrease in carbamazepine concentrations: CYP3A4 induction; decrease in efavirenz concentrations: CYP3A4 and CYP2B6 induction)	Co-administration with Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should be avoided unless plasma concentrations of carbamazepine and efavirenz can be monitored
Phenytoin, Phenobarbital, and other anticonvulsants that are substrates of CYP isozymes	No interaction study available. Possible reduction or increase in the plasma concentrations of phenytoin, phenobarbital and other anticonvulsants that are substrates of CYP isozymes with efavirenz.	Co-administration should be avoided unless plasma concentrations of the anticonvulsants and efavirenz can be monitored
Valproic acid (250 mg b.i.d) / efavirenz	No clinically significant effect on efavirenz pharmacokinetics. Limited data suggest there is no clinically significant effect on valproic acid pharmacokinetics	Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets and alproic acid can be co-administered without dose adjustment..
Vigabatrin Gabapentin You must 53 also use a reliable barrier method of contraception (see Pregnancy and breast-feeding). Atripla may make hormonal contraceptives less likely to work	Interaction not studied. Clinically significant interactions are not expected since vigabatrin and gabapentin are exclusively eliminated unchanged in the urine and are unlikely to compete for the same metabolic enzymes and elimination pathways as efavirenz.	Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets and vigabatrin can be co-administered without dose adjustment
ANTICOAGULANTS		
Warfarin / Efavirenz **Acenocoumarol**/Efavirenz	No interaction study available. Coadministration may decrease (and less likely increase) warfarin exposure	Monitor INR. Dose adjustments of warfarin may be necessary.
ANTIDEPRESSANTS		
Selective Serotonin Reuptake Inhibitors (SSRIs)		
Sertraline/Efavirenz (50 mg q.d./600 mg q.d.)	Sertraline: AUC: ↓ 39% Cmax: ↓ 29% Cmin: ↓ 46% Efavirenz: AUC: ↔ Cmax: ↑ 11% Cmin: ↔ (CYP3A4 induction)	When co-administered with Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, sertraline dose increases should be guided by clinical response.
Paroxetine/Efavirenz (20 mg q.d./600 mg q.d.)	Paroxetine: AUC: ↔ Cmax: ↔ Cmin: ↔ Efavirenz: AUC: ↔ Cmax: ↔ Cmin: ↔	Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets and paroxetine can be co-administered without dose adjustment.
Fluoxetine/Efavirenz	Interaction not studied. Since fluoxetine shares a similar metabolic profile with paroxetine, i.e. a strong CYP2D6 inhibitory effect, a similar lack of interaction would be expected for fluoxetine.	Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets and fluoxetine can be co-administered without dose adjustment.
Norepinephrine and dopamine reuptake inhibitor		
Bupropion [150 mg single dose (sustained release)]/efavirenz	Bupropion: AUC: ↓55% Cmax: ↓34% Hydroxybupropion: AUC: ↔ Cmax: ↑50% (CYP2B6 induction)	Increases in bupropion dosage should be guided by clinical response, but the maximum recommended dose of bupropion should not be exceeded. No dose adjustment is necessary for efavirenz.
CARDIOVASCULAR AGENTS		
Calcium channel blockers		
Diltiazem (240 mg q.d.) / efavirenz (600 mg q.d.)	Diltiazem: AUC: ↓ 69% Cmax: ↓60% Cmin: ↓ 63% Desacetyl diltiazem: AUC: ↓75% Cmax: ↓64% Cmin: ↓ 62% N-monodesmethyl diltiazem: AUC: ↓37% Cmax: ↓ 28% Cmin: ↓37% Efavirenz: AUC: ↑ 11% Cmax: ↑ 16% Cmin: ↑ 13% (CYP3A4 induction) The increase in efavirenz pharmacokinetic parameters is not considered clinically significant.	Monitor the clinical effect of diltiazem and increase dose if necessary.
Verapamil, felodipine, nifedipine, nicardipine / efavirenz	Interaction not studied. Exposure of a calcium channel blocker that is a substrate of CYP3A4 enzyme is likely to be lowered in cotreatment with efavirenz.	Monitor clinical effect and increase calcium channel blocker dose if necessary
LIPID LOWERING AGENTS		
HMG Co-A Reductase Inhibitors		
Atorvastatin (10 mg q.d) / efavirenz (600 mg q.d.)	Atorvastatin: AUC: ↓ 43% Cmax: ↓ 12% 2-hydroxy atorvastatin: AUC: ↓35% Cmax: ↓ 13% 4-hydroxy atorvastatin: AUC: ↓ 4% Cmax: ↓ 47% Total active moiety: AUC: ↓ 34% Cmax: ↓ 20%	Cholesterol levels should be periodically monitored and the dose of atorvastatin increased in case of insufficient efficacy.
Pravastatin (40 mg q.d.) / efavirenz (600 mg q.d.)	Pravastatin: AUC: ↓ 40% Cmax: ↓ 18%	Cholesterol levels should be periodically monitored and the dose of pravastatin increased in case of insufficient efficacy.
Simvastatin 40 mg q.d.) / efavirenz (600 mg q.d.)	Simvastatin: AUC: ↓69% Cmax: ↓ 76% Simvastatin acid: AUC: ↓ 58% Cmax: ↓ 51% Total active moiety: AUC: ↓ 60% Cmax: ↓ 62% (CYP3A4 induction) Co-administration of efavirenz with atorvastatin, pravastatin, or simvastatin did not affect efavirenz AUC or Cmax values	Cholesterol levels should be periodically monitored and the dose of simvastatin increased in case of insufficient efficacy.
Rosuvastatin / efavirenz (600 mg q.d.)	Interaction not studied. Rosuvastatin is largely excreted unchanged via the faeces, therefore metabolic drug interaction with efavirenz is not expected.	Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets can be co-administered with rosuvastatin without dose adjustment..
HORMONAL CONTRACEPTIVES		
Ethinyloestradiol/norgestimate (0.035 mg + 0.25 mg q.d) / Efavirenz (600 mg q.d.)	No change in ethinylestradiol exposure. Levonorgestrel AUC ↓ 83% Cmax: ↓80% Cmin: ↓86% (induction of metabolism) Norelgestromin AUC ↓ 64% Cmax: ↓ 46% Cmin: ↓82% (active metabolites). Efavirenz : no clinically significant interaction.	A reliable method of barrier contraception should be used in addition to oral contraceptives.
DMPA (150 mg i.m. single dose) / efavirenz (600 mg q.d.)	The pharmacokinetics and efficacy of DMPA was not altered due to cotreatment with efavirenz	Because of the limited information available, a reliable method of barrier contraception should be used in addition to hormonal contraception.
Levonorgestrel (implant) /efavirenz (600 mg q.d.)	A randomized,parallel group study showed that in HIV infected women with LNG implants who were administered EFV as part of their ART LNG levels were reduced by 57% at 48 weeks. In addition, contraceptive failure was observed in 15% (3/20 subjects) in this group.	A reliab le method of barrier contraception should be used in addition to hormonal contraception.
Etonogestrel (implant) / efavirenz (600 mg q.d.)	Interaction not studied. ↓ 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 should be used in addition to hormonal contraception.

Dimensions: L x W (500 x 650)

IMMUNOSUPPRESSANTS		
Immunosuppressants metabolised by CYP3A4 (e.g. cyclosporine, tacrolimus, sirolimus)/ efavirenz	Interaction not formally studied. exposure of these immunosuppressants may be expected (CYP3A4). These immunosuppressants are not anticipated to impact exposure of 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 and tenofovir disoproxil fumarate tablets.
OPIOIDS		
Methadone / efavirenz (600 mg q.d.)	Methadone AUC ↓ 52% Cmax: ↓ 45% (CYP3A4 induction) In a study of HIV infected intravenous drug users, coadministration of efavirenz with methadone resulted in decreased plasma levels of methadone and signs of opiate withdrawal. The methadone dose was increased by a mean of 22% to alleviate withdrawal symptoms.	Monitor for withdrawal symptoms and increase methadone dose if necessary.
Buprenorphine / efavirenz (600 mg q.d.)	Buprenorphine AUC ↓ 50%; norbuprenorphine AUC ↓71% Efavirenz : No clinically significant pharmacokinetic interaction.	Despite the decrease in buprenorphine exposure, no patients exhibited withdrawal symptoms. Dose adjustment of buprenorphine may not be necessary when co-administered with Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets..

Studies conducted with other medicinal products

There were no clinically significant pharmacokinetic interactions when efavirenz was administered with azithromycin, cetirizine, fosamprenavir/ritonavir, lorazepam, zidovudine, aluminium/magnesium hydroxide antacids, famotidine or fluconazole. The potential for interactions with efavirenz and other azole antifungals, such as ketoconazole, has not been studied.

There were no clinically significant pharmacokinetic interactions when lamivudine was administered with stavudine, zidovudine or famciclovir.

There were no clinically significant pharmacokinetic interactions when tenofovir disoproxil was co- administered with emtricitabine or ribavirin.

4.6 Pregnancy and lactation

Pregnancy

Efavirenz: Cases of neural tube defects in infants born to women with first trimester exposure have been reported. A systematic review and meta-analysis of observational cohorts reported birth outcomes among women exposed to efavirenz during the first trimester. The analysis found no increased risk of overall birth defects among a fair amount women (over 2,000 pregnancy outcomes) exposed to efavirenz compared with exposure to other antiretroviral drugs. However, risks to the fetus cannot be ruled out. Studies of efavirenz in animals have shown reproductive toxicity, including marked teratogenic effects (see section 5.3).

Tenofovir disoproxil and lamivudine

Animal studies do not indicate direct or indirect harmful effects of tenofovir disoproxil or lamivudine with respect to reproductive toxicity (see section 5.3). 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).

The use of Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets may be considered during pregnancy.

Breast-feeding

Efavirenz, lamivudine and tenofovir have been shown to be excreted in human milk. There is insufficient information on the effects of efavirenz, lamivudine and tenofovir in newborns/infants. A risk to the suckling child cannot be excluded.

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.

Fertility

No clinical data on the effect of Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are available. Animal studies do not indicate harmful effects of efavirenz, lamivudine or tenofovir disoproxil on fertility (see section 5.3).

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. 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 tenofovir disoproxil.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 and tenofovir disoproxil fumarate tablets, taking also into account their seriousness and the number of reports.

Metabolic and nutrition disorders
Very common: hypophosphataemia
Common: increases in fasting triglycerides, total cholesterol, high-and low density lipoprotein cholesterol, hyperglycaemia
Uncommon: hypokalaemia, hypercholesterolaemia
Rare: lactic acidosis

Blood and lymphatic system disorders
Uncommon: neutropentia, anaemia, thrombocytopenia
Very rare: pure red cell aplasia

Vascular disorders
Uncommon: flushing

Immune system disorders
Uncommon: hypersensitivity

Nervous system disorders
Very common: dizziness
Common: abnormal dreams, insomnia, disturbance in attention,somnolence, cerebellar coordination and balance disturbances, headache
Uncommon: agitation, amnesia, ataxia, abnormal coordination, confusional state, convulsions, abnormal thinking, tremor
Very rare: peripheral neuropathy (or paraesthesia)

Psychiatric disorders
Common: anxiety and depression
Uncommon: affect lability, aggression, euphoric mood, hallucination, mania, paranoia, suicide attempt, suicide ideation, psychosis
Rare: neurosis*, delusion*, completed suicide*

Hepatobiliary disorders
Common: elevation of liver enzymes
Uncommon: acute hepatitis
Rare: hepatic failure*, hepatic steatosis

Skin and subcutaneous tissue disorders
Very common: rash
Common: pruritus, hair loss
Uncommon: erythema multiforme, angioedema, Stevens-Johnson syndrome
Rare: photoallergic dermatitis

Musculoskeletal and connective tissue disorders
Uncommon: rhabdomyolysis, muscular weakness, myalgia, arthralgia, myopathy
Rare: osteomalacia (manifested as bone pain and infrequently contributing to fractures)*

Reproductive system and breast disorders
Uncommon: gynaecomastia

Eye disorders
Uncommon: blurred vision

Ear and labyrinth disorders
Uncommon: vertigo, tinnitus

Respiratory, thoracic and mediastinal disorders:
Common: cough, nasal symptom

Gastrointestinal disorders
Very common: diarrhoea, vomiting, nausea
Common: elevated serum lipase, elevated amylase including elevated pancreatic amylase, abdominal pain, dyspepsia, flatulence, anorexia
Uncommon: pancreatitis

Renal and urinary disorders:
Uncommon: increased creatinine, proteinuria
Rare: renal failure (acute and chronic), proximal renal tubulopathy including Fanconi syndrome, acute tubular necrosis nephritis (including acute interstitial nephritis)*, nephrogenic diabetes insipidus

General disorders and administration site disorders
Very common: asthenia
Common: fatigue, malaise, fever
Not known: immune reconstitution syndrome (see section 4.4)

* These adverse reactions were identified through post-marketing surveillance for either efavirenz, lamivudine or tenofovir disoproxil. The frequency category was estimated from a statistical calculation based on the total number of patients treated with any of the components of this fixed dose combination.

Description of selected adverse reactions

Rash

In clinical trials of efavirenz, rashes were usually mild-to-moderate maculopapular skin eruptions that occurred within the first two weeks of initiating therapy with efavirenz. In most patients, rash resolved with continuing therapy with efavirenz within one month. Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets can be reinitiated in patients interrupting therapy because of rash. Use of appropriate antihistamines and/or corticosteroids is recommended when treatment is restarted.

Renal impairment:

As Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets may cause renal damage, monitoring of renal function is recommended (see sections 4.4). Proximal renal tubulopathy generally resolved or improved after discontinuation of therapy. However, in some patients, declines in creatinine clearance did not completely resolve despite discontinuation. Patients at risk of renal impairment (such as patients with baseline renal risk factors, advanced HIV disease, or patients receiving concomitant nephrotoxic medications) are at increased risk of experiencing incomplete recovery of renal function (see section 4.4).

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: 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 the use efavirenz, lamivudine and tenofovir disoproxil in the absence of proximal renal tubulopathy.

Psychiatric symptoms

Patients with a history of psychiatric disorders appear to be at greater risk of serious psychiatric adverse reactions.

Nervous system symptoms

Nervous system symptoms are common with efavirenz. 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 and tenofovir disoproxil fumarate 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 and 4.4).

Hepatic failure with efavirenz

Hepatic failure, including cases in patients with no pre-existing hepatic disease or other identifiable risk factors, as reported post-marketing, were sometimes characterized by a fulminant course, progressing in some cases to transplantation or death.

Interaction with didanosine

Co-administration of Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets and didanosine is not recommended as it results in a 40-60% increase in systemic exposure to didanosine that may increase the risk of didanosine-related adverse reactions (see section 4.5). Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported.

Metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment (see section 4.4).

In HIV infected patients with severe immune deficiency at the time of initiation of CART, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Osteonecrosis:

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to CART. The frequency of this is unknown (see section 4.4).

Special populations

HIV/HBV co-infected patients

In HIV infected patients co-infected with HBV, clinical and laboratory evidence of hepatitis may occur after discontinuation of treatment (see section 4.4).

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

4.9 Overdose

Efavirenz

Symptoms

Some patients accidentally taking efavirenz 600 mg twice daily, have reported increased nervous system symptoms. One patient experienced involuntary muscle contractions.

Treatment

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. 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.

Lamivudine

Symptoms

Limited data are available on the consequences of ingestion of acute overdoses of lamivudine in humans. No fatalities occurred, and the patients recovered. No specific signs or symptoms have been identified following such overdose.

Treatment

There is no known specific treatment for overdose with EPIVIR. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required. Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event.

Tenofovir

Approximately 10% of the tenofovir dose can be removed by haemodialysis. It is not known whether tenofovir can be removed by peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for treatment of HIV infections, combinations, ATC code: J05AR

Mechanism of action and pharmacodynamic effects

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

Lamivudine, the negative enantiomer of 2'-deoxy-3'-thiacytidine, is a dideoxynucleoside analogue.

Tenofovir disoproxil 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.

In-vitro data tend to suggest that the continuation of lamivudine in an antiretroviral regimen despite the development of M184V might provide residual anti-retroiral 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 anti-retroviral 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 M184Vmutation. 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. The K65R mutation can also be selected by abacavir or didanosine and results in reduced susceptibility to these agents plus lamivudine, emtricitabine and tenofovir. The K65R mutation remains fully susceptible to efavirenz. In addition, a K70E substitution in HIV-1 RT has been selected by tnoovir and results in low-level reduced susceptibility to abacavir, emtricitabine, lamivudine and tenofovir.

Patients whose HIV expressed 3 or more TAMs that included either the M41L or L210W mutation showed reduced response to tenofovir.

Clinical results:

When tenofovir and lamivudine were combined with efavirenz in treatment-naive 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, lamivudine 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 Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets in healthy volunteers, mean (SD) efavirenz C_{max} value was 2.48 μg/ml (± 0.75 μg/ml) and the corresponding value for $AUC_{0-\infty}$ was 53.0 μg·h/ml (± 14.1 μg·h/ml). The median efavirenz t_{max} value was 3.21 hours (± 1.25 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. Bioavailabiliy is between 80 and 85%. Following single dose administration of Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets in healthy volunteers, the mean (SD) Lamivudine C_{max} value was 2303 ng/ml (± 543 ng/ml) and the corresponding value for AUC was 11935 ng•h/ml (± 22852 ng•h/ml). The mean (SD) lamivudine T_{max} value was 1.83 hours (± 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

The active moiety, intracellular lamivudine triphosphate, has a prolonged terminal half-life in the cell (16 to 19 hours) compared to the plasma lamivudine half-life (5 to 7 hours). In 60 healthy adult volunteers, lamivudine 300 mg once daily has been demonstrated to be pharmacokinetically equivalent at steady-state to lamivudine 150 mg twice daily with respect to intracellular triphosphate AUC_{24} and C_{max}. 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 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

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 to HIV infected patients, tenofovir disoproxil is rapidly absorbed and converted to tenofovir. The oral bioavailability of tenofovir from tenofovir disoproxil in fasted patients was approximately 25%. Administration of tenofovir disoproxil with a high fat meal enhanced the oral bioavailability, with an increase in tenofovir AUC by approximately 40% and Cmax by approximately 14%.

Following single dose administration of Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets in healthy volunteers, the mean (SD) tenofovir C_{max} value was 320 ng/ml (± 106 ng/ml) and the corresponding value for AUC was 2631 ng•h/ml (± 684 ng•h/ml). The mean (SD) tenofovir t_{max} value was 1.22 hours (± 0.63 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 25.0 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 nor tenofovir are substrates for the CYP450 enzymes.

Special populations

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 disoproxil 245 mg was similar to exposures achieved in adults receiving once-daily doses of tenofovir disoproxil 245 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 245 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 2.19 (12%) μg·h/ml in subjects with CrCl > 80 ml/min to respectively 3.06 (30%) μg·h/ml, 6.01 (42%) μg·h/ml and 15.99 (45%) μg·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 Cmin 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 Cmax of 1.03 μg/ml and a mean AUC0-48h of 42.86 μg·h/ml. It is recommended that the dosing interval for tenofovir disoproxil 245 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 245 mg dose of tenofovir disoproxil 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 Cmax and $AUC_{0-\infty}$ values were 0.22 (34.8%) μg/ml and 2.05 (50.8%) μg·h/ml, respectively, in normal subjects compared with 0.29 (46.0%) μg/ml and 2.31 (43.5%) μg·h/ml in subjects with moderate hepatic impairment, and 0.31 (24.8%) μg/ml and 2.74 (44.0%) μg·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 tumors in female mice, but not in male mice.

Lamivudine

Non-clinical data on lamivudine reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, carcinogenic potential and toxicity to reproduction and development. 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.

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 reduced the viability index and weight of pups in peripost natal toxicity studies. Genotoxicity studies have shown that tenofovir disoproxil 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 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 was also weakly positive in an in vivo / in vitro unscheduled DNA synthesis test in primary rat hepatocytes.

Tenofovir disoproxil 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 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:

Lactose anhydrous, Croscarmellose sodium, Hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, pregelatinized starch, sodium lauryl sulfate, sodium starch glycolate and Iron oxide yellow.

Film-coating:

"Opadry II white 85F18422" comprised of polyvinyl alcohol-part hydrolised, titanium dioxide, macrogol / PEG and talc.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package. Keep the bottle tightly closed.

6.5 Nature and contents of container

30's Count:

White opaque 120 cc HDPE bottle containing Cansorb IT 3g Silica gel canister closed with 38 mm- 400 ARGUS CR closure with TEKNIPLEX HS 123 induction sealing wad.

90's Count:

White opaque 250 cc HDPE bottle containing Cansorb IT 3g Silica gel canister closed with 53 mm- 400 ARGUS CR closure with TEKNIPLEX HS 123 induction sealing wad.

6.6 Special precautions for disposal and other handling

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

7. Supplier

Laurus Labs Limited
2nd Floor, Serene Chambers, Road No.-7
Banjara Hills, Hyderabad – 500034.
India.

8. WHO PREQUALIFICATION REFERENCE NUMBER

Not applicable

9. DATE OF PREQUALIFICATION

Not applicable

10. DATE OF REVISION OF THE TEXT

April 2019

Pharmacological class: 7.13 Antivirals

Prescription Preparations (P.P.):

Botswana Reg. No.:
NAFDAC Reg. No.:
Tanzania Reg. No.:
Zambia Reg. No.:
Zimbabwe Reg. No.:

PATIENT INFORMATION LEAFLET: INFORMATION FOR THE USER

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

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

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

What is in this leaflet

1. What Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are and what it is used for
2. What you need to know before you take Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets
3. How to take Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets Possible side effects
4. How to store Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets
5. Contents of the pack and other information

1. What Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are and what it is used for

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets is a combination of three antiviral medicines used to treat Human Immunodeficiency Virus (HIV) infection in adults and adolescents. Antiviral medicines used for HIV infection are known as *antiretrovirals*.

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets contains the active substances:

- efavirenz, a non-nucleoside reverse transcriptase inhibitor
- lamivudine, a nucleoside reverse transcriptase inhibitor
- tenofovir disoproxil, a nucleotide reverse transcriptase inhibitor

These substances block an enzyme (reverse transcriptase) that is used by HIV for making copies of itself. By doing so, they prevent the reproduction of the virus.

This medicine is not a cure for HIV infection. While taking Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets Tablets you may still develop infections or other illnesses associated with HIV infection.

2. What you need to know before you take Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets

Do not take Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets

- are allergic (hypersensitive) to efavirenz, lamivudine, tenofovir disoproxil or any of the other ingredients of Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets listed at the end of this leaflet (section 6).
- are currently taking any of the following medicines:
  - **astemizole or terfenadine** (used to treat hay fever or other allergies)
  - **bepridil** (used to treat heart disease)
  - **cisapride** (used to treat heartburn)
  - **ergot alkaloids** (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine) (used to treat migraines and cluster headaches)
  - **midazolam or triazolam** (used to help you sleep)
  - **pimozide** (used to treat certain mental conditions)
  - **tenofovir alafenamide**
  - **voriconazole** (a drug used against fungal infections)
  - **dasabuvir + ombitasvir/paritaprevir/ritonavir** (a combination of medicines used to treat infection with hepatitis C virus)
  - **St. John´s wort** (*Hypericum perforatum*, a herbal remedy used for depression and anxiety).

If this applies to you, tell your health care provider immediately. Taking these medicines with Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets could cause serious or life-threatening side effects or stop these medicines from working properly.

Take special care with Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets :

Talk to your health care provider before taking Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets .You will need to take this medicine every day. It helps to control your condition, but it is not a cure for HIV infection. You may continue to develop other infections and other illnesses associated with HIV disease. You can still pass on HIV to others through sexual contact or contamination with blood when taking this medicine. You must continue to take precautions to avoid this.

You should keep in regular contact with your health care provider. Do not stop taking your medicine without first talking to your health care provider.

Tell your health care provider if you:

- **are taking other medicines** that contain efavirenz, lamivudine, tenofovir disoproxil, or emtricitabine or adefovir dipivoxil. Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should not be taken with any of these medicines.
- **have or have had kidney disease**, or if tests have shown problems with your kidneys. This medicine may affect your kidneys. Before starting this medicine you may need blood tests to check how well your kidneys are working. Blood tests may also be required during treatment to check the health of your kidneys.
- **have a history of mental illness**, including depression, or of substance or alcohol abuse. Tell your health care provider immediately if you feel depressed, have suicidal thoughts or have strange thoughts (see section 4, *Possible side effects*).
- **have a history of convulsions (fits or seizures)** or if you are being treated with anticonvulsant therapy such as carbamazepine, phenobarbital and phenytoin. If you are taking any of these medicines, your health care provider may need to check the level of anticonvulsant medicine in your blood to ensure that it is not affected while taking Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets.
- **have a history of liver disease, including chronic active hepatitis.** Patients with liver disease including chronic hepatitis B or C, who are treated with combination antiretrovirals, have a higher risk of severe and potentially life-threatening liver problems. If you have hepatitis B infection, your health care provider will carefully consider the best treatment regimen for you. Your health care provider may conduct blood tests to check how well your liver is working.

Once you start taking Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, look out for:

- **signs of dizziness, difficulty sleeping, drowsiness, difficulty concentrating or abnormal dreaming.** These side effects may start in the first 1 or 2 days of treatment and usually go away after the first 2 to 4 weeks.
- **any signs of skin rash.** Rashes may be caused Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. If you see any signs of a severe rash with blistering or fever, stop taking this medicine and tell your health care provider at once.
- **any signs of inflammation or infection.** In some patients with advanced HIV infection (AIDS) and a history of AIDS-associated (opportunistic) infection, signs and symptoms of inflammation from such previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please tell your health care provider at once.

  In addition, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. These may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, irregular heartbeats, trembling or shaking, or hyperactivity, please inform your health care provider at once.
- **any signs of bone problems.** Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The duration of antiretroviral therapy, use of a corticosteroid such as dexamethasone or prednisolone, alcohol consumption, severe suppression of the immune system, and being overweight may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these, tell your health care provider.

  Bone problems (sometimes resulting in fractures) may also occur due to damage to the kidney cells (see section 4, *Possible side effects*). The growth of bone could be affected when adolescents that are not fully grown use Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets. If you are an adolescent, your health care provider may check your growth and may take precautionary measures.

Taking other medicines and Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets

You must not take Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets with certain medicines. **Tell your health care provider immediately if you are taking** astemizole or terfenadine **(used to treat hay fever or other allergies)**, bepridil **(used to treat heart disease)**, cisapride **(used to treat heartburn)**, ergot alkaloids **(for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine) (used to treat migraines and cluster headaches)**, midazolam or triazolam **(used to help you sleep)**, pimozide **(used to treat certain mental conditions)**, voriconazole **(a drug used against fungal infections)**, dasabuvir + ombitasvir/paritaprevir/ritonavir **(a combination of medicines used to treat nfection with hepatitis C virus)**, St. John's wort **(*Hypericum perforatum*, a herbal remedy used for depression and anxiety) (see section: *do not take Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets if you*).**

Tell your health care provider if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Also, Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should not be taken with other medicines that contain efavirenz (unless recommended by your health care provider), lamivudine, tenofovir, or emtricitabine or adfovir dipivoxil.

Tell your health care provider if you are taking other medicines that may damage your kidneys. These include:

- aminoglycosides or vancomycin (medicines for bacterial infections)
- amphotericin B or pentamidine (medicines for fungal infections)
- foscarnet, ganciclovir, or cidofovir (medicines for viral infections)
- tacrolimus (for suppression of the immune system)
- interleukin-2 (used to treat cancer)
- non-steroidal anti-inflammatory drugs (NSAIDs, to relieve bone or muscle pains)

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets may interact with other medicines, including herbal preparations such as Ginkgo biloba extracts. As a result, the amounts of Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets or other medicines in your blood may be affected. This may stop your medicines from working properly, or may make any side effects worse. In some cases, your health care provider may need to adjust your dose or check your blood levels. **It is important to tell your health care provider if you are taking any of the following:**

- **Medicines containing didanosine (for HIV infection):** Taking Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets with medicines that contain didanosine can raise the levels of didanosine in your blood. Rarely, inflammation of the pancreas and lactic acidosis (excess lactic acid in the blood), which sometimes caused death, has been reported when medicines containing tenofovir disoproxil and didanosine were taken together. Combining tenofovir with didanosine can also reduce the effects of antiretroviral therapy.

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets may also interact with the following medicines and may make any side effects worse or may impact on the either agent's efficacy:

- **amprenavir, atazanavir, darunavir, etravirine, fosamprenavir, indinavir, lopinavir, maraviroc, nevirapine, ritonavir, saquinavir** and **tipranavir** (medicines used to treat HIV infection)
- **boceprevir, daclatasvir, simeprevir** and **telaprevir** (used to treat infection with hepatitis C virus)
- **methadone, buprenorphine** (medicines used for severe pain or opiate addiction)
- **clarithromycin, rifabutin and rifampicin** (medicines used to treat bacterial infections and tuberculosis)
- **atorvastatin, pravastatin, or simvastatin** (medicines used to lower blood fats, also called statins)
- **hormonal contraceptives** such as birth control pills, an injected contraceptive or a contraceptive implant. Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets may make hormonal contraceptives less likely to work. You must, therefore, also use a reliable barrier method of contraception (e.g. condoms), if you are taking this medicine.
- **itraconazole, posaconazole** (medicines used to treat fungal infections) **lumefantrine/artesunate, atovaquone/proguanil, amodiaquine/artesunate, quinine, halofantrine, artemisinins** (medicines used to treat malaria)
- **carbamazepine, phenytoin** (medicines used to treat convulsions/seizures (epilepsy))
- **diltiazem, verapamil, felodipine, nifedipine, nicardipine** (medicines called calcium channel blockers, used to treat high blood pressure and conditions related to the heart)
- **tacrolimus, cyclosporine, sirolimus** (medicines used to prevent organ transplant rejection, also called immunosuppressants)
- **sertraline** (medicine used to treat depression)
- **warfarin** and **acenocoumarol** (medicines used to reduce clotting of the blood)
- **bupropion** (medicine used for smoking cessation)

Pregnancy and breast-feeding Pregnancy

Tell your health care provider if you are pregnant or trying to become pregnant. Your health care provider can explain the risks and benefits of your therapy to you and your child.

Breastfeeding

If you are interested in breastfeeding your baby, you should discuss the risks and benefits with your healthcare provider.

Driving and using machines

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets may cause dizziness, impaired concentration, and drowsiness. If you experience these symptoms, do not drive and do not use any tools or machines.

Important information about some of the ingredients of Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance (e.g. galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption) may experience symptoms of intolerance when using it.

3. How to take Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets

Always take Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets exactly as your health care provider. Check with your health care provider if you are not sure.

Always take the dose recommended by your health care provider. Do not change the dose unless your health care provider tells you to.

The recommended dose is:

One tablet taken each day by mouth. Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should be taken on an empty stomach (1 hour before or 2 hours after a meal). It may help to take the tablet at bedtime, as this can make some side effects (for example, dizziness, drowsiness) less troublesome. The tablet should be taken with water and swallowed whole.

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets must be taken every day.

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets should not be used by children under 10 years of age or weighing less than 35 kg.

If your health care provider decides to stop, or change the dose of, one of the components of Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, you may be given efavirenz, lamivudine and/or tenofovir separately or with other medicines for the treatment of HIV infection.

If you take more Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets than you should:

If you accidentally take too many Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, you may be at increased risk of experiencing possible side effects with this medicine (see section 4, possible side effects). Contact your health care provider or the nearest emergency department for advice. Take the tablet container with you so that you can easily describe what you have taken.

If you forget to take Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets:

It is important not to miss a dose.

If you do miss a dose within 12 hours of when it is usually taken, take it as soon as you can, and then take your next dose at its regular time.

If it is almost time (less than 12 hours) for your next dose anyway, do not take the missed dose. Wait and take the next dose at the regular time. Do not take a double dose to make up for a forgotten tablet.

If you throw up within 1 hour of taking Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, you should take another tablet. Do not wait until your next dose is due. You do not need to take another tablet if you threw up more than an hour after taking Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600 mg/300 mg/300 mg Tablets.

If you stop taking Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets:

Don't stop taking this medicine without talking to your health care provider. Stopping this medicine can seriously affect your response to future treatment. If Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets is stopped, speak to your health care provider before you restart taking these tablets. Your health care provider may consider giving you the components of Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets separately if you are having problems or need your dose adjusted.

When your supply of Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets starts to run low, get more from your health care provider. This is very important because the amount of virus may start to increase if the medicine is stopped for even a short time. The virus may then become harder to treat.

If you have both HIV infection and hepatitis B, it is especially important not to stop your Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets treatment without talking to your health care provider first. Some patients have had blood tests or symptoms indicating that their hepatitis got worse after stopping treatment. Your health care provider may recommend that you resume hepatitis B treatment if you stop Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets treatment. You may require blood tests to check how your liver is working for 4 months after stopping treatment. In some patients with advanced liver disease or cirrhosis, stopping treatment is not recommended as this may lead to worsening of your hepatitis, which may be life-threatening.

Tell your health care provider immediately about new or unusual symptoms after you stop treatment, particularly symptoms you associate with hepatitis B infection.

If you have any further questions on the use of this product, ask your health care provider.

4. Possible side effects

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your health care provider will test for these changes.

Like all medicines, Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets can cause side effects, although not everybody gets them.

Possible serious side effects:

Lactic acidosis (excess lactic acid in the blood) is a **rare**, but serious side effect that can be life- threatening. If you get any of the following symptoms, **tell your health care provider immediately**:

- deep rapid breathing
- drowsiness
- feeling sick (nausea), being sick (vomiting) and stomach pain.

Other potentially serious side effects:

If you think that you may have any of these serious side effects, talk to your health care provider. The following side effects are **uncommon** (these may affect up to 1 in every 100 patients):

- allergic reaction (hypersensitivity) that may cause severe skin reactions (Stevens-Johnson syndrome, erythema multiforme, see section 2)
- swelling of the face, lips, tongue or throat
- angry behaviour, suicidal thoughts, strange thoughts, paranoia, unable to think clearly, mood being affected, seeing or hearing things that are not really there (hallucinations), suicide attempts, personality change (psychosis)
- pain in the abdomen (stomach), caused by inflammation of the pancreas
- forgetfulness, confusion, fitting (seizures), incoherent speech, tremor (shaking)
- yellow skin or eyes, itching, or pain in the abdomen (stomach) caused by inflammation of the liver

Psychiatric side effects in addition to those listed above include delusions (false beliefs), neurosis. Some patients have committed suicide. These problems tend to occur more often in those who have a history of mental illness. Always notify your health care provider immediately if you have these symptoms.

Side effects to the liver: If you are also infected with hepatitis B virus, you may experience a worsening of hepatitis after stopping treatment (see section 3 *How to take* Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets).

The following side effects are **rare** (these may affect up to 1 in every 1000 patients):

- back pain caused by kidney problems, including kidney failure. Your health care provider may do blood tests to see if your kidneys are working properly.
- inflammation of the kidney, passing a lot of urine and feeling thirsty, damage to kidney tubule cells
- fatty liver
- liver failure, in some cases leading to death or liver transplant. Most cases occurred in patients who already had liver disease, but there have been a few reports in patients without any existing liver disease.
- softening of the bones (withbone pain and sometimes resulting in fractures)

Most frequent side effects

The following side effects are **very common** (these may affect more than 1 user in every 10 patients):

- dizziness, diarrhoea, feeling sick (nausea), being sick (vomiting)
- rashes (including red spots or blotches sometimes with blistering and swelling of the skin), which may be allergic reactions
- feeling weak

Tests may also show:

- decreases in phosphate levels in the blood

Other possible side effects

The following side effects are **common** (these may affect up to 1 user in every 10):

- stomach pain
- difficulty sleeping, abnormal dreams, difficulty concentrating, drowsiness
- feeling worried or depressed
- problems with digestion resulting in discomfort after meals, feeling bloated, wind (flatulence)
- loss of appetite
- tiredness
- itching
- hair loss
- disturbances of coordination and balance
- headache
- cough
- irritated or runny nose
- fever (high temperature)
- general feeling of being unwell

Tests may also show:

- increased fatty acids (triglycerides) or sugar levels in the blood
- liver and pancreas problems

The following side effects are **uncommon** (these may affect up to 1 user in every 100 patients):

- blurred vision
- a feeling of spinning or tilting (vertigo), whistling, ringing or other persistent noise in the ears
- flushing
- breast enlargement in males
- breakdown of muscle, muscle pain or weakness

Tests may also show:

- low white blood cell count that help defend against infections and low red blood cell count (anaemia)
- low red blood cell count (thrombocytes) that help to stop bleeding
- increased cholesterol in the blood
- decreases in potassium in the blood
- increases in creatinine in the blood
- proteins in urine

The breakdown of muscle, softening of the bones (with bone pain and sometimes resulting in fractures), muscle pain, muscle weakness and decreases in potassium or phosphate in the blood may occur due to damage to kidney tubule cells..

The following side effects are **rare** (these may affect up to 1 in every 1,000 patients)

- itchy rash to the skin caused by a reaction to sunlight

The following side effects are **very rare** (these may affect up to 1 user in every 10,000 patients)

- a failure of the bone marrow to produce new red blood cells (pure red cell aplasia)
- tingling or numbness of the arms, legs, hands or feet

If you get any side effects, talk to your health care provider. This includes any possible side effects not listed in this leaflet. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets

Keep out of the reach and sight of children.

Do not use Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets after the expiry date which is stated on the bottle and carton after (EXP). The expiry date refers to the last day of that month.

Store below 30°C.

Medicines should not be disposed of via wastewater or household waste. Ask your health care provider how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets contain

The active ingredients are 600 mg efavirenz, 300 mg lamivudine, 300 mg tenofovir disoproxil fumarate 300 mg (equivalent to 245 mg of tenofovir disoproxil tenofovir).

The other ingredients are: anhydrous lactose, croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, pregelatinized starch, sodium lauryl sulphate, Purified water and for the film coat: macrogol/PEG, polyvinyl alcohol, talc and titanium dioxide.

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets contains lactose. Patients with rare hereditary problems of galactose intolerance (e.g. galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption) may experience symptoms of intolerance when using it.

What Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets look like and contents of the pack

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets are white coloured, capsule shaped, biconvex film coated tablets debossed with 'L65' on one side and plain on the other side.

30's Count: White opaque 120 cc HDPE bottle containing Cansorb IT 3g Silica gel canister closed with 38 mm- 400 ARGUS CR closure with TEKNIPLEX HS 123 induction sealing wad.

90's Count: White opaque 250 cc HDPE bottle containing Cansorb IT 3g Silica gel canister closed with 53 mm- 400 ARGUS CR closure with TEKNIPLEX HS 123 induction sealing wad.

Marketing Authorization Holder and Manufacturer

Marketing Authorization Holder:
Laurus Labs Limited,
2nd Floor, Serene Chambers, Road No.-7,
Banjara Hills, Hyderabad, Telangana – 500034.
India.

Manufacturer:

Laurus Labs Limited, (Unit-2),
Plot No:19, 20 & 21, Western Sector, APSEZ,
Atchutapuram Mandal,
Visakhapatnam-District-531011,
Andhra Pradesh, India.

This leaflet was last revised in 16/04/2019