SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 600 mg efavirenz, 300 mg lamivudine and 300 mg tenofovir disoproxil fumarate (TDF) equivalent to 245 mg of tenofovir disoproxil or 136 mg of tenofovir.

Excipients with known effect

Each film-coated tablet contains 199.6 mg of lactose monohydrate. Each film-coated tablet contains 43 mg of sodium.
For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablets
Yellow coloured, capsule shaped, biconvex, film coated tablets with “T” debossed on one side and plain on the other side.

4. CLINICAL PARTICULARS

a. Therapeutic indications

Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets is a fixed dose combination of efavirenz, lamivudine and tenofovir disoproxil fumarate. 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/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets to treat antiretroviral experienced patients with HIV-1 infection should be based on individual viral resistance testing and/or the treatment history of the patient.

Consideration should be given to official treatment guidelines for HIV-1 infection (e.g. by WHO,http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf).

b. Posology and method of administration

Posology

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

Adults and adolescents

The recommended dose of Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300

mg/300 mg tablets is one tablet taken orally once daily.

Missed dose and vomiting after a dose

It is important that the patient takes the medicine regularly as prescribed. Missing doses can increase the risk of resistance to Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mgtablets 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 patients vomit within 1 hour of taking Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg 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 asusual when it is due.

Dose adjustments and discontinuation of therapy

Where discontinuation of therapy with one of the components of Efavirenz/Lamivudine/Tenofovirdisoproxil fumarate 600 mg/300 mg/300 mg tablets is indicated or where dose modification is necessary, separate preparations of efavirenz, lamivudine and tenofovir disoproxil fumarate are available. Please refer to the Summary of Product Characteristics for these medicinal products.

If therapy with Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg 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/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets are co-administered with rifampicin in patients weighing ≥ 50 kg, an additional 200 mg/day (800 mg total) ofefavirenz may be considered (see section 4.4 and 4.5).

Special populations

Elderly: Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets shouldbe administered with caution to elderly patients (see section 4.4).

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

Hepatic impairment: Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets is 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/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets to these patients(see sections 4.4, 4.5 and 5.2).

Paediatric population

Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets are not recommended for use in children below 10 years of age or weighing less than 35 kg since appropriatedose adjustments cannot be made with this combination tablet.

Method of administration

Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg 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/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets should preferably be taken before bedtime, in order to improve the tolerability of efavirenz with respect toundesirable effects on the nervous system (see section 4.8).

c. Contraindications

Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets is 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/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg 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/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg 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 Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets due to the risk of decreased plasma concentrations and reduced clinical effects of efavirenz (see section 4.5).

d. Special warnings and precautions for use

Concomitant use of other medicinal products

As a fixed combination, Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets should not be administered concomitantly with other medicinal products containing any of the same active components, efavirenz, lamivudine or tenofovir disoproxil fumarate. 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/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets should not beadministered concomitantly with adefovir dipivoxil.

Co-administration of Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets and didanosine is not recommended since exposure to didanosine is significantly increased following co-administration with tenofovir disoproxil fumarate (see section 4.5). Rarely, pancreatitisand lactic acidosis, sometimes fatal have been reported.

No data are available on the safety and efficacy of combined efavirenz, lamivudine and tenofovirdisoproxil fumarate 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/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg 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/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg 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 antiretroviraltherapy (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 timesthe upper limit of normal, interruption or discontinuation of treatment with Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg 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 hepatoxicity 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 HIVinfection in patients co-infected with HBV or HCV.

Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at anincreased risk for severe and potentially fatal hepatic adverse reactions.

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

Lamivudine and tenofovir disoproxil fumarate are also active against HBV. Therefore, discontinuationof Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg 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 fumarate. 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 predictiveof 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 require 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/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg 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/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg 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 fumarate are primarily excreted by the kidneys, through a combination of glomerular filtration and active tubular secretion. Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg 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 fumarate 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 fumarate 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/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg 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/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets is 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 andtenofovir disoproxil fumarate 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 nephrotoxicagents 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 fumarate.

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 fumarate treatment group than in the comparator group treated withstavudine (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 wasno 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 shouldbe 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 ofbone 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, decidethe 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 fumarate- 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 fumarate-associated changes in BMD on long-term bone health andfuture fracture risk are currently unknown.

If bone abnormalities are detected or suspected in paediatric patients, consultation with anendocrinologist 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 andpain, 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 relatingthis 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 HIV-negative infants exposed *in utero* and/or postnatally to nucleoside analogues. The main adverse events reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactataemia, hyperlipasaemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether the neurological disorders are transient or permanent is currently unknown. Any child exposed *in utero* to nucleoside and nucleotide analogues, even HIV-negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. These findings do not affect current national recommendations to use antiretroviral therapyin 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 weeksor months after initiation of combination ART, an inflammatory reaction to asymptomatic or residualopportunistic 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/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg 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/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets be taken on anempty stomach, preferably at bedtime.

General

Transmission of HIV: while effective viral suppression with antiretroviral therapy has been proven tosubstantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions toprevent 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 ahealth care providers experienced in the treatment of HIV infection.

Excipients

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicinal product contains 9.1 mmol (43 mg) sodium per tablet. To be taken into considerationby patients on a controlled sodium diet.

e. Interaction with other medicinal products and other forms of interaction

No drug interaction studies have been performed using Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets. As this medicine contains efavirenz, lamivudine and tenofovir disoproxil fumarate, any interactions that have been identified with these agents individuallymay occur with this combination tablet. Interaction studies with these agents have only been performed in adults.

Contraindications of concomitant use

Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg 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/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets is a fixed-dose combination product, the dose of efavirenz cannot be altered; therefore, voriconazole and Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg 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/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets is 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/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets and St. John's wort or herbal preparations containing St. John's wort is contraindicated. Plasmalevels 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).

<u>Concomitant use not recommended</u>

As a fixed combination, Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets should not be administered concomitantly with other medicinal products containing the components, lamivudine or tenofovir disoproxil as fumarate. Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg 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 othercytidine analogues, such as emtricitabine.

Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets should not beadministered 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 (seesection 4.4).

In vitro and clinical pharmacokinetic interaction studies have shown that the potential for CYP-mediated interactions involving lamivudine and tenofovir disoproxil fumarate with other

medicinalproducts 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 or 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/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets. Therefore, co-administration of atazanavir/ritonavir and Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets is not recommended (see Table 1).

Didanosine

Co-administration of Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mgtablets and didanosine is not recommended (see section 4.4 and Table 1).

Posaconazole

Concomitant use of posaconazole and Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg 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/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg 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/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg 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).

<u>Cannabinoid test interaction</u>

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/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg 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**	**Recommendations concerning co-administration**
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/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets should not be co-administered, due to the
Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
		similarity between emtricitabine and lamivudine, and consequently expected lack of additive effects (see section 4.4.).
Didanosine (400 mg q.d.) / tenofovir	Didanosine AUC □ 40-60%	The risk of didanosine-related adverse effects (e.g., pancreatitis, lactic acidosis) appears to be increased, and CD4 cells may decrease significantly on co-administration. Also didanosine at 250 mg co-administered with tenofovir within several different antiretroviral combination regimens has been associated with a high rate of virological failure.

		Co-administration of Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg 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 **Fosamprenavir/ritonavir** (1400/200 mg q.d.) / efavirenz	amprenavir C_{trough} □ 17% No significant interaction with twice daily regimen at steady state. Amprenavir C_{min}: □ 36% at steady state	No dose adjustment necessary. Avoid concomitant use of Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets and once-daily fosamprenavir regimen.
Saquinavir HCG/ritonavir (1000/100mg b.i.d) / efavirenz	No clinically relevant interaction was noted.	Insufficient data are available for making a dosing recommendation for saquinavir, with or without ritonavir, when co-administered with Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets. Co- administration with saquinavir, with or without ritonavir, is not recommended.
Indinavir (800 mg t.i.d) / efavirenz(200 mg q.d)	Indinavir AUC □ 31%, C_{trough} □ 40%	Concomitant use with unboosted indinavir isnot recommended.

Indinavir/ritonavir (800/100 mg b.i.d.) / efavirenz	Indinavir AUC_{ss} □ 25% C_{trough} □ 50%	Concomitant use with boosted indinavir is only recommended when it is possible to monitor the plasma concentration of indinavir.
Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
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** (400 mg/100 mg b.i.d.)/tenofovir (300 mg q.d)	Substantial decrease in lopinavir exposure. Lopinavir C_{min} □ □ 40% Lopinavir concentrations: similar to lopinavir/ritonavir 400/100 mg twice daily without efavirenz Lopinavir/ritonavir: No significant effect on	Insufficient data are available to make a dosing recommendation for lopinavir/ritonavir when dosed with Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets. Co-administration of lopinavir/ritonavir and Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets is not recommended.

	lopinavir/ritonavir PK parameters. Tenofovir: AUC: ↑ 32% C_{max}: ↔ C_{min}: ↑ 51%	
Atazanavir 400mg / efavirenz **Atazanavir** (400 mg q.d.)/ tenofovir	Atazanavir AUC_{ss}: □ 74% C_{min}: □ 93% Atazanavir: AUC: ↓ 25% C_{max}: ↓ 21% C_{min}: ↓ 40% Tenofovir:	Concomitant use of Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets and unboosted atazanavir is not recommended.

Medicinal products by therapeuticareas	Interaction	Recommendations concerning co-administration
	AUC: ↑ 24% C_{max}: ↑ 14% C_{min}: ↑ 22%	
Atazanavir/ritonavir/Tenofovir disoproxil fumarate (300 mg q.d./100mg q.d./300 mg q.d.) **Atazanavir/ritonavir**/Efavirenz (400 mg q.d./100 mg q.d./600 mg q.d., all administered with food)	Atazanavir: AUC: ↓ 25% C_{max}: ↓ 28% C_{min}: ↓ 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%*	Co-administration of atazanavir/ritonavir and Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets is not recommended.

Atazanavir/ritonavir/Efavirenz (400 mg q.d./200 mg q.d./600 mg q.d., all administered with food)	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 C_{min} might negatively impact the efficacy of atazanavir. ** based on historical	
Medicinal products by therapeuticareas	**Interaction**	**Recommendations concerning co-administration**
	comparison. Co-administration of efavirenz with atazanavir/ritonavir is not recommended.	

Tipranavir/ritonavir / efavirenz	Appropriate data on the interaction between the approved tipranavir regimen and efavirenz are lacking.	The combination of Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg 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 (300mg q.d)	Darunavir AUC_{ss} □ 13% Cmax □ 15% C_{min} □ 31%. (CYP3A4 induction) Efavirenz AUC □ 21% C_{max} □ 15% C_{min} □ 17% (CYP3A4 induction) Darunavir: No significant effect on darunavir/ritonavir PK parameters. Tenofovir: AUC: ↑ 22% C_{min}: ↑ 37%	Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets in combination with darunavir/ritonavir 800/100mg once daily may result in suboptimal darunavir C_{min}. If Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg 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 caution in combination with Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg 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% C_{max}: □ 51% Maraviroc AUC_{12h}: □	Refer to the SmPC for the medicinal product containing maraviroc.

	C_{max}: □ Tenofovir concentrations not measured, no effect is expected.	
Medicinal products by therapeuticareas	**Interaction**	**Recommendations concerning co-administration**
Integrase strand transfer inhibitors		
Raltegravir (400 mg single dose) /efavirenz **Raltegravir** (400 mg b.i.d.) /tenofovir	Raltegravir AUC □ 36% C_{max}: ↓ 36% (UGT1A1 induction) Raltegravir AUC ↑ 49% C_{max} ↑ 64% Tenofovir AUC: ↓ 10% C_{max}: ↓ 23%	Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets and raltegravir can be co-administered without dose adjustment.
ANTIVIRALS AGAINST HBV		
Adefovir dipivoxil / tenofovir	AUC: ↔ C_{max}: ↔	Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets should not be administered concurrently with adefovir dipivoxil due to an expected lack of additive effect (see section 4.4).
Entecavir (1 mg q.d.)	AUC: ↔ C_{max}: ↔	No clinically significant pharmacokinetic interactions when Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg 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%* C_{max}:↔ 8% C_{min}:↓ 44% Efavirenz: AUC:↔ 20% C_{max}:↔ 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.
Medicinal products by therapeuticareas	**Interaction**	**Recommendations concerning co-administration**
Telaprevir (1,125 mg q8h)/Efavirenz(600 mg q.d.)	Telaprevir (relative to 750 mg q8h): AUC: ↓18% C_{max}: ↓14% C_{min}: ↓25% Efavirenz: AUC: ↓18% C_{max}: ↓24% C_{min}: ↓10% (CYP3A	If Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets and telaprevir are co-administered, telaprevir 1,125 mg every 8 hours should be used.

	induction by efavirenz)	
Simeprevir/Efavirenz (150 mgq.d./600 mg q.d.)	Simeprevir: AUC: ↓ 71% C_{max}: ↓ 51% C_{min}: ↓ 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/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets is not recommended.
Daclatasvir (60 mg q.d./120 mg q.d.) / Efavirenz 600 mg q.d.	↓ Daclatasvir AUC*: 0.68 C_{max}*: 0.83 C_{min}*: 0.41 Induction of CYP3A4 by efavirenz *results are dose- normalised to 60 mgdose.	The dose of daclatasvir should be increased to 90 mg once daily when coadministered with Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets

Dasabuvir + ombitasvir/paritaprevir/ritonavir / Efavirenz/emtricitabine/tenofovir disoproxil fumarate 600/300/200 mgq.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/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets is contraindicated.
Medicinal products by therapeuticareas	**Interaction**	**Recommendations concerning co-administration**
Sofosbuvir / Efavirenz (600 mg q.d.) **Sofosbuvir** / Tenofovir disoproxil fumarate (300 mg q.d.)	No clinically significant pharmacokinetic interaction No clinically significant pharmacokinetic interaction	No dose adjustment required for eithermedicinal product.
ledipasvir (90 mg once daily) / **sofosbuvir** (400 mg once daily) / Efavirenz/ emtricitabine/ tenofovir disoproxil fumarate (600 mg/ 200 mg/300 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 eithermedicinal product.
ANTIMYCOBACTERIALS AND ANTIBIOTICS		

Clarithromycin (500 mg b.i.d, multiple doses) / efavirenz	Clarithromycin AUC □ 39% C_{max} □ 26% 14-OH-chlaritromycin AUC □ 34% C_{max} □ 49% Efavirenz AUC □ C_{max} □ 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 eithermedicinal product.
Rifampicin (600 mg q.d, multipledoses)/ efavirenz	Efavirenz AUC □ 26%, C_{max} □ 20% C_{min} □ 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/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets.
Medicinal products by therapeuticareas	**Interaction**	**Recommendations concerning co-administration**
Rifabutin (300 mg q.d) / efavirenz	Rifabutin AUC □ 38% C_{max} □32% C_{min} □ 45%	Increase rifabutin dose by 50% if co-treating with Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mgtablets.

ANTIFUNGALS		
Fluconazole (200 mg q.d.) / efavirenz(400 mg q.d.)	No clinically significant interaction	No dose adjustment is necessary for eithermedicinal product.
Itraconazole (200 mg b.i.d) / efavirenz (600 mg q.d.)	Itraconazole AUC_{ss} □ 39%, C_{max} □37% C_{min} □ 44% Hydroxyitraconazole AUC □ 37%, C_{max} □35% C_{min} □ 43%	Consider alternative antifungal agent, or useTDM if available.
Posaconazole (400 mg b.i.d.) / efavirenz (400 mg q.d.)	Posaconazole: AUC □50% C_{max} □ 45%	Concomitant use of posaconazole and Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets should be avoided.
Voriconazole (200 mg b.i.d) /efavirenz (400 mg q.d)	Voriconazole: AUC: ↓ 77% C_{max}: ↓ 61% Efavirenz: AUC: ↑ 44% C_{max}: ↑ 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/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets, these must not be co-administered with voriconazole.
ANTIMALARIALS		

Chloroqui ne **Mefloquin e** **Proguanil** **Sulfadoxi ne** **Pyrimethamine** / efavirenz	No formal interaction studies available. Drug interactions and safety in coadministrati on with efavirenz has not been systematically evaluated; on a theoretical basis,	
Medicinal products by therapeuticareas	**Interaction**	**Recommendations concerning co-administration**
	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. Co- administration of amodiaquine and Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets should be avoided.

Quinine / efavirenz	No formal interaction study available. Quinine is extensively metabolised by CYP3A. Co-administration 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/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets.
Lumefantrine Halofantrine / efavirenz	No formal interaction studies available. These agents are metabolised by CYP3A; hence, co- treatment with efavirenz may decrease exposure.	Co-treatment with Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets may decrease antimalarial efficacy. When co-treating caution is recommended.
Medicinal products by therapeuticareas	**Interaction**	**Recommendations concerning co-administration**

Artemether/Lumefantrine/Efavirenz (20/120 mg tablet, 6 doses of 4 tablets each over 3 days/600 mg q.d.)	Artemether: AUC: ↓ 51% C_{max}: ↓ 21% Dihydroartemisinin (active metabolite): AUC: ↓ 46% C_{max}: ↓ 38% Lumefantrine: AUC: ↓ 21% C_{max}: ↔ Efavirenz: AUC: ↓ 17% C_{max}: ↔ (CYP3A4 induction)	Co-treatment with Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets may decrease antimalarial efficacy. When co-treating 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% C_{max}: ↓44% Proguanil: AUC: ↓43% Cmax: ↔	Concomitant administration of atovaquone/proguanil with Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets should be avoided whenever possible.
ANTICONVULSANTS		
Carbamazepine (400 mg q.d) / efavirenz (600 mg q.d.)	Carbamazepine: AUC: ↓ 27% C_{max}: ↓ 20% C_{min}: ↓ 35% Efavirenz:	Co-administration with Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets should be avoided unless plasma concentrations of carbamazepine and efavirenz can be monitored.
Medicinal products by therapeuticareas	**Interaction**	**Recommendations concerning co-administration**
	AUC: ↓ 36% Cmax: ↓ 21% Cmin: ↓ 47% (decrease in carbamazepine concentrations: CYP3A4 induction; decrease in efavirenz concentrations: CYP3A4 and CYP2B6 induction)	

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 pharmacokinetic s. Limited data suggest there is no clinically significant effect on valproic acid pharmacokinetic s.	Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg 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 (efavirenz/emtricitabine/tenofo vir disoproxil fumarate) may make hormonal contraceptives less likely towork	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/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets and vigabatrin can be co-administered without dose adjustment.

Medicinal products by therapeuticareas	Interaction	Recommendations concerning co-administration
ANTICOAGULANTS		
Warfarin / efavirenz **Acenocoumarol**/Efavirenz	No interaction study available. Co-administration may decrease (and less likely increase) warfarin exposure.	Monitor INR. Dose adjustments of warfarinmay be necessary.
ANTIDEPRESSANTS		
Selective Serotonin Reuptake Inhibitors (SSRIs)		
Sertraline/Efavirenz (50 mg q.d./600mg q.d.)	Sertraline: AUC: ↓ 39% C_{max}: ↓ 29% C_{min}: ↓ 46% Efaviren z: AUC: ↔ C_{max}: ↑ 11% C_{min}: ↔ (CYP3A4 induction)	When co-administered with Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets, sertraline dose increases should be guided byclinical response.
Paroxetine/Efavirenz (20 mgq.d./600 mg q.d.)	Paroxetin e: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Efaviren z: AUC: ↔ C_{max}: ↔ C_{min}:	Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg 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/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg 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% C_{max}: ↓34% Hydroxybupropion:	Increases in bupropion dosage should be guided by clinical response, but the maximum recommended dose of bupropion should not beexceeded. No dose adjustment is necessary for efavirenz.
Medicinal products by therapeuticareas	**Interaction**	**Recommendations concerning co-administration**
	AUC: ↔ C_{max}: ↑50% (CYP2B6 induction)	
CARDIOVASCULAR AGENTS		
Calcium channel blockers		

Diltiazem (240 mg q.d.) / efavirenz(600 mg q.d.)	Diltiazem: AUC: □ 69% C_{max}: □ 60% C_{min}: □ 63% Desacetyl diltiazem: AUC: □75% C_{max}: □ 64% C_{min}: □ 62% N-monodesmethyldiltiazem: AUC: □37% C_{max}: □ 28% C_{min}: □ 37% Efavirenz: AUC: ↑ 11% C_{max}: ↑ 16% C_{min}: ↑ 13% (CYP3A4 induction) The increase in efavirenz pharmacokinetic parameters is not considered clinically significant.	Monitor the clinical effect of diltiazem andincrease 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 co-treatment with	Monitor clinical effect and increase calcium channel blocker dose if necessary

	efavirenz.	
Medicinal products by therapeuticareas	**Interaction**	**Recommendations concerning co-administration**
LIPID LOWERING AGENTS		
HMG Co-A Reductase Inhibitors		
Atorvastatin (10 mg q.d) / efavirenz(600 mg q.d.)	Atorvastatin: AUC: □ 43% C_{max}: □ 12% 2-hydroxy atorvastatin: AUC: □ 35% C_{max}: □ 13% 4-hydroxy atorvastatin: AUC: □ 4% C_{max}: □ 47% Total active moiety: AUC: □ 34% C_{max}: □ 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% C_{max}: □ 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.)	Simvastati n: AUC: □ 69% C_{max}: □ 76% Simvastatin acid: AUC: ↓ 58% C_{max}: ↓ 51% Total active moiety: AUC: □ 60% C_{max}: □ 62% (CYP3A4 induction) Co-administration of efavirenz with atorvastatin, pravastatin, or simvastatin did not affect efavirenz AUC or C_{max} values.	Cholesterol levels should be periodically monitored and the dose of simvastatin increased in case of insufficient efficacy.
Rosuvastatin / efavirenz (600 mgq.d.)	Interaction not studied. Rosuvastatin is largely excreted	Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets can be co-administered with rosuvastatin without

Medicinal products by therapeuticareas	Interaction	Recommendations concerning co-administration
	unchanged via the faeces; therefore metabolic drug interaction with efavirenz is not expected.	dose adjustment.
HORMONAL CONTRACEPTIVES		
Ethinyloestradiol/norgestimate (0.035 mg + 0.25 mg q.d) / efavirenz(600 mg q.d.)	No change in ethinylestradiolexposure. Levonorgestrel AUC □ 83% C_{max}: □ 80% C_{min}: □ 86% (induction of metabolism) Norelgestromin AUC □ 64% C_{max}: □ 46% C_{min}: □ 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 co-treatment 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 reliable method of barrier contraception should be used in addition to hormonal contraception.
Medicinal products by therapeuticareas	**Interaction**	**Recommendations concerning co-administration**
Etonogestrel (implant) / efavirenz(600 mg q.d.)	Interaction notstudied. □ exposure of etonogestrel may be expected due to the CYP3A induction of efavirenz. There have been occasional postmarketing	A reliable method of barrier contraception should be used in addition to hormonal contraception.

	reports of contraceptive failure with etonogestrel in efavirenz-exposed patients	
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/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets.
OPIOIDS		

Methadone / efavirenz (600 mg q.d.)	Methadone AUC □ 52% C_{max}: ↓ 45% (CYP3A4 induction) In a study of HIV infected intravenous drug users, co-administration 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%	Despite the decrease in buprenorphine exposure, no patients exhibited withdrawal symptoms. Dose adjustment of buprenorphine may not be necessary when co-administered

Medicinal products by therapeuticareas	Interaction	Recommendations concerning co-administration
	Efavirenz : No clinically significant pharmacokinetic interaction.	with Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mgtablets.

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 administeredwith stavudine, zidovudine or famciclovir.

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

f. Pregnancy, lactation and fertility

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 woman (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 fumarate and lamivudine

Animal studies do not indicate direct or indirect harmful effects of tenofovir disoproxil fumarate or lamuvidine 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/Tenofovir disoproxil fumarate tablet may be considered duringpregnancy.

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. Arisk 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/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets are available. Animal studies do not indicate harmful effects of efavirenz, lamivudine or tenofovir disoproxil fumarate on fertility (see section 5.3).

g. Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, dizziness has been reported during treatment with efavirenz and tenofovir disoproxil fumarate.

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

h. 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 fumarate.

The adverse events considered at least possibly related to the treatment are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000), very rare (<1/10,000). In addition, adverse events identified during post-approval use are listed (frequency category: 'not known'). Since they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been included for their potential causal connection to the active components of Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg 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 fumarate. 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.

<u>Description of selected adverse reactions</u>

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/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg 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/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg 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 fumarate: rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), hypokalaemia, muscular weakness, myopathy and hypophosphataemia. These events are not considered to be causally associated with the use efavirenz, lamivudine and tenofovir disoproxil fumarate 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 duringthe first one or two days of efavirenz therapy and generally resolve after the first two to four weeks. They may occur more frequently when Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg 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/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg 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 lifestyle. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relatingthis to any particular treatment (see section 4.4).

Immune Reactivation Syndrome

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 (seesection 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 of suspected adverse reactions

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.

i. 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 beenidentified following such overdose.

Treatment

There is no known specific treatment for overdose with lamivudine. 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 whethertenofovir can be removed by peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

a. 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 notinhibited by efavirenz.

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

Tenofovir disoproxil fumarate is converted *in vivo* to tenofovir, a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate. Lamivudine and tenofovir are phosphorylated bycellular 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 willalso 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 reducedsusceptibility). 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 viralfitness). 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 mutationshowed reduced response to tenofovir.

<u>Clinical results</u>

When tenofovir and lamivudine were combined with efavirenz in treatment-naïve patients with HIV-1,the proportion of patients (ITT) with HIV-RNA <50 copies/ml were 76.3% and 67.8% at 48 and 144 weeks, respectively.

No specific studies with the combination tenofovir, lamivudine and efavirenz have been conducted inadolescents.

b. 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 plasmaconcentrations were reached in 6 - 7 days.

Following single dose of administration of Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg tablets in healthy volunteers, mean (SD) efavirenz C_{max} value was 3.112

µg/ml (0.752 µg/ml) and the corresponding value for AUC_{0-72h} was 61.667 µg·h/ml (16.044 µg·h/ml).The median efavirenz t_{max} value was 3.71 hours (1.24 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 efavirenzin 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 inductionof 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 than1% 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/Tenofovir disoproxil fumarate

600 mg/300 mg/300 mg tablets in healthy volunteers, the mean (SD) Lamivudine C_{max} value was 2.865 µg/ml (0.747 µg/ml) and the corresponding value for AUC_{0-72h} was 12.934 µg·h/ml (2.998 µg·h/ml). The mean (SD) lamivudine T_{max} value was 1.38 hours (0.50 hours).

Co-administration of lamivudine with food results in a delay of t_{max} and a lower C_{max} (decreased by47%). 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 lowdue 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 fumarate

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

Absorption

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

Administration of tenofovir disoproxil fumarate with a high fat meal enhanced the oral bioavailability, with an increase in tenofovir AUC by approximately 40% and Cmax by approximately 14%.

Following single dose administration of Efavirenz/Lamivudine/Tenofovir disoproxil fumarate

600 mg/300 mg/300 mg tablets in healthy volunteers, the mean (SD) tenofovir C_{max} value was 0.336 µg/ml (0.082 µg/ml) and the corresponding value for AUC_{0-72h} was 2.311 µg·h/ml (0.654 µg·h/ml). The mean (SD) tenofovir t_{max} value was 1.02 hours (0.30 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 oftenofovir is approximately 12 to 18 hours.

Studies have established the pathway of active tubular secretion of tenofovir to be influx into proximaltubule cell by the human organic anion transporters (hOAT) 1 and 3 and efflux into the urine by the multidrug resistant protein 4 (MRP 4). *In vitro* studies have determined that neither tenofovir disoproxil fumarate nor tenofovir are substrates for the CYP450 enzymes.

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 300 mg wassimilar to exposures achieved in adults receiving once-daily doses of tenofovir 300 mg.

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

Renal impairment: Pharmacokinetic parameters of tenofovir were determined following administration of a single dose of tenofovir disoproxil fumarate 300 mg to 40 non-HIV, non-HBV infected patients with varying degrees of renal impairment defined according to baseline creatinine clearance (CrCl) (normal renal function when CrCl > 80 ml/min; mild with CrCl = 50-79 ml/min; moderate with CrCl = 30-49 ml/min and severe with CrCl = 10-29 ml/min). Compared with patients with normal renal function, the mean (%CV) tenofovir exposure increased from 2.19 (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, betweendialysis 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 fumarate 300 mg is modified in patients with creatinine clearance < 50 ml/min or in patients who already have ESRD and require dialysis (see section 4.2).

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

Hepatic impairment

A single 300 mg dose of tenofovir disoproxil fumarate was administered to non-HIV, non-HBV infected patients with varying degrees of hepatic impairment defined according to Child-Pugh-Turcotte (CPT) classification. Tenofovir pharmacokinetic parameters were not substantially altered in subjects with hepatic impairment suggesting that no dose adjustment is required in these subjects. Themean (%CV) tenofovir Cmax and AUC0-∞ 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 restingperipheral 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 andpulmonary 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 fumarate reduced the viability index and weight of pups in peripost natal toxicity studies. Genotoxicity studies have shown that tenofovir disoproxil fumarate was negative in the in vivo mouse bone marrow micronucleus assay but was positive for inducing forward mutations in the in vitro L5178Y mouse lymphoma cell assay in the presence or absence of S9 metabolic activation.

Tenofovir disoproxil fumarate was positive in the Ames test (strain TA 1535) in two out of three studies, once in the presence of S9 mix (6.2- to 6.8-fold increase) and once without S9 mix. Tenofovirdisoproxil fumarate was also weakly positive in an in vivo / in vitro unscheduled DNA synthesis test in primary rat hepatocytes. Tenofovir disoproxil fumarate did not show any carcinogenic potential in a long-term oral carcinogenicity study in rats. A long-term oral carcinogenicity study in mice showed a low incidence of duodenal tumours, considered likely related to high local concentrations of tenofovir disoproxil fumarate in the gastrointestinal tract at a dose of 600 mg/kg/day. While the mechanism of tumour formation is uncertain, the findings are unlikely to be of relevance to humans.

6. PHARMACEUTICAL PARTICULARS

a. List of excipients

Core tablet: Croscarmellose sodium Hydroxypropylcellul seLactose Magnesium stearate Microcrystalline cellulose

Pregelatinized starch Sodium lauryl sulphateIron oxide yellow

Film coat:
Hypromellose
Polyvinyl alcohol – part hydrolysedTalc
Titanium dioxide Macrogol /PEG
Lecithin (soya) Iron oxide yellow

b. Incompatibilities

Not applicable.

c. Shelf life

24 months

6.3 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

HDPE bottle with non-child resistant cap, containing 3 x 1 gm silica gel bag or 1 x 3 gm silica gel bag.Pack size: 30 tablets.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORIZATION HOLDER AND MANUFACTURER NAME & ADDRESS

Cipla Quality Chamical Industries Limited, Plot 1-7, 1st Ring Road, Luzira Inductrial Park, Uganda

8. MARKETING AUTHORIZATION NUMBER

Rwanda FDA-HMP-MA-0059

9. DATE OF FIRST AUTORISATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization: 01/06/2021

10. DATE OF REVISION OF THE TEXT

August 2016