SUMMARY OF PRODUCT CHARACTERISTICS

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1. NAME OF THE MEDICINAL PRODUCT

Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate Tablets 400 mg/300 mg/300 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains Efavirenz USP 400 mg, lamivudine USP 300 mg and Tenofovir disoproxil fumarate 300 mg equivalent to 245 mg of tenofovir disoproxil.

Each tablet contains 217 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White to off-white, film-coated, oval, biconvex tablets debossed with "L40"on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets is a fixed dose combination of efavirenz, lamivudine and tenofovir disoproxil. It is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in patients weighing at least 30 kg.

Treatment regimens should follow most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

4.2 Posology and method of administration

Posology

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

Adults and adolescents weighing at least 30 kg

The recommended dose of Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate is one tablet taken orally once daily.

Special populations

Elderly

Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate should be administered with caution to elderly patients (see section 4.4).

Dose adjustments

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

Renal impairment

Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate 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 that cannot be achieved with the combination tablet (see sections 4.4 and 5.2).

Hepatic impairment

Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate 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 (see sections 4.3, 4.4 and 5.2). Patients should be monitored carefully for adverse reactions, especially nervous system symptoms related to efavirenz.

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

If therapy with Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate 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.

Paediatric population

Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate are not recommended for use in patients weighing less than 30 kg since appropriate dose adjustments cannot be made with this combination tablet.

Method of administration

Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate is administered orally and 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 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).

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 and Tenofovir Disoproxil fumarate and reduce its effectiveness.

If the patient misses a dose and it is less than 12 hours after it was due, the patient should be advised to take the dose as soon as possible and then take the next dose at the scheduled time. 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 , 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.

4.3 Contraindications

Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate is contraindicated in patients with clinically significant hypersensitivity to efavirenz, lamivudine or tenofovir, or to any of the excipients contained in the formulation.

Severe hepatic impairment (CPT, Class C) (see section 5.2).

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).

Co-administration with elbasvir (EBR) and grazoprevir (GZR) due to the potential for significant decreases in plasma concentrations of EBR and GZR (see section 4.5).

Voriconazole and Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate 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 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 and Tenofovir Disoproxil fumarate due to the risk of decreased plasma concentrations and reduced clinical effects of efavirenz (see section 4.5).

Patients with:

- a family history of sudden death or of congenital prolongation of the QTc interval on electrocardiograms, or with any other clinical condition known to prolong the QTc interval.

- a history of symptomatic cardiac arrythmias or with clinically relevant bradycardia or with congestive cardiac failure accompanied by reduced left ventricle ejection fraction.

- severe disturbances of electrolyte balance e.g. hypokalemia or hypomagnesemia.

Patients taking drugs that are known to prolong the QTc interval (proarrythmic). These drugs include:

- antiarrhythmics of classes IA and III,

- neuroleptics, antidepressive agents,

- certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole and triazole antifungal agents,

- certain non-sedating antihistamines (terfenadine, astemizole),

- cisapride,

- flecainide,

- certain antimalarials,

- methadone.

4.4 Special warnings and precautions for use

General

HBV antibody testing should be offered to all individuals before initiating therapy with lamivudine and tenofovir disoproxil-containing therapies (see below "Patients with HIV and hepatitis B (HBV) or C virus (HCV) co-infection").

Concomitant use of other medicinal products

As a fixed combination, Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate should not be administered concomitantly with other medicinal products containing any of the same active components, efavirenz, lamivudine or tenofovir disoproxil.

Due to similarities with lamivudine, Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate should not be administered concomitantly with other cytidine analogues, such as emtricitabine. Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate should not be administered concomitantly with medicinal products containing adefovir dipivoxil or tenofovir alafenamide.

Co-administration of Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate 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.

The combination of lamivudine with cladribine is not-recommended (see section 4.5).

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

Co-administration with amodiaquine is not recommended since amodiaquine exposure significantly increased following co-administration with efavirenz. Hepatotoxicity has been observed (see section 4.5).

Co-administration with bedaquiline is not recommended, since plasma concentrations of bedaquiline decreased due to CYP3A induction by efavirenz, which may result in loss of therapeutic effect of bedaquiline (see section 4.5).

The safety and efficacy of Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate TB/ HIV-coinfected patients using rifampicin have not been established. Insufficient data are available to make a dosing recommendation for rifampicin in combination with Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate . Therefore co-administration of rifampicin and Efavirenz,

Lamivudine and Tenofovir Disoproxil fumarate is not recommended.

Antivirals against HCV

Co-administration with simeprevir is not recommended, since plasma concentrations of simeprevir significantly decreased due to CYP3A induction by efavirenz, which may result in loss of therapeutic effect of simeprevir (see section 4.5).

Co-administration with sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir is not recommended, since plasma concentrations of velpatasvir significantly decreased due to CYP3A induction by efavirenz, which may result in loss of therapeutic effect of velpatasvir.

Co-administration of tenofovir disoproxil with ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir has been shown to increase plasma concentrations of tenofovir. Tenofovir-associated adverse reactions should be monitored in patients receiving ledipasvir/sofosbuvir and Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate .

Co-administration of glecaprevir/pibrentasvir with efavirenz may significantly decrease plasma concentrations of glecaprevir and pibrentasvir, leading to reduced therapeutic effect. Coadministration of glecaprevir/pibrentasvir with efavirenz is not recommended.

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 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 disease

The pharmacokinetics, safety and efficacy of Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate have not been established in patients with significant underlying liver disorders (see section 5.2).

Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate is contraindicated in patients with severe hepatic impairment (see section 4.3) and not recommended in patients with moderate hepatic impairment. Since efavirenz is principally metabolised by the CYP system, caution should be exercised in administering Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate to patients with mild hepatic impairment. These patients should be carefully monitored for efavirenz adverse reactions, especially nervous system symptoms (see section 4.2). Laboratory tests should be

performed to evaluate their liver disease at periodic intervals.

Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy (CART) and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Liver toxicity

Hepatic failure has occurred in patients with no pre-existing hepatic disease or other identifiable risk factors, who were treated with efavirenz (see section 4.8). Liver enzyme monitoring should be considered for patients without pre-existing hepatic dysfunction or other risk factors.

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

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

Healthcare providers should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with HBV.

In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant summary of product characteristics for these medicinal products.

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 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.

Exacerbations of hepatitis

Flares on treatment: Spontaneous exacerbations in chronic hepatitis B are relatively common and are characterised by transient increases in serum ALT. After initiating antiviral therapy, serum ALT may increase in some patients (see section 4.8). In patients with compensated liver disease, these increases in serum ALT are generally not accompanied by an increase in serum bilirubin concentrations or hepatic decompensation. Patients with cirrhosis may be at a higher risk for hepatic

decompensation following hepatitis exacerbation, and therefore should be monitored closely during therapy.

Flares after treatment discontinuation: Acute exacerbation of hepatitis has also been reported in patients who have discontinued hepatitis B therapy. Post-treatment exacerbations are usually associated with rising HBV DNA, and the majority appears to be self-limited. However, severe exacerbations, including fatalities, have been reported. Hepatic function should be monitored at repeated intervals with both clinical and laboratory follow-up for at least 6 months after discontinuation of hepatitis B therapy. If appropriate, resumption of hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation. Liver flares are especially serious, and sometimes fatal in patients with decompensated liver disease.

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.

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.

Late-onset neurotoxicity, including ataxia and encephalopathy (impaired consciousness, confusion, psychomotor slowing, psychosis, delirium), may occur months to years after beginning efavirenz therapy. Effects may be severe or life-threatening, but are generally reversible on discontinuation. Events of late-onset neurotoxicity have occurred in patients with CYP2B6 genetic polymorphisms that are associated with increased efavirenz levels despite daily dosages of 600 mg of efavirenz. Patients presenting with signs and symptoms of serious neurological adverse events should be evaluated promptly to assess the possibility that these events may be related to efavirenz use, and whether discontinuation of Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate is warranted.

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 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 . 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 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 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 and Tenofovir Disoproxil fumarate and nephrotoxic agents is unavoidable, renal function must be monitored weekly (see section 4.5).

Tenofovir disoproxil has not been clinically evaluated in patients receiving medicinal products which are secreted by the same renal pathway, including the transport proteins human organic anion transporter (hOAT) 1 and 3 or MRP 4 (e.g. cidofovir, a known nephrotoxic medicinal product). These renal transport proteins may be responsible for tubular secretion and in part, renal elimination of tenofovir and cidofovir. Consequently, the pharmacokinetics of these medicinal products, which are secreted by the same renal pathway including transport proteins hOAT 1 and 3 or MRP 4, might be modified if they are coadministered. Unless clearly necessary, concomitant use of these medicinal products which are secreted by the same renalpathway is not recommended, but if such use is unavoidable, renal function should 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.

Rash

Mild-to-moderate rash has been reported with the individual components of Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate . 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 and Tenofovir Disoproxil fumarate 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 is not recommended for patients who have had a life-threatening cutaneous reaction (e.g., Stevens-Johnson syndrome) while taking an NNRTI.

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.

In HIV-1 infected adolescents 12 years of age and older, the mean rate of bone gain was less in the tenofovir disoproxil-treated group compared to the placebo group. Skeletal growth (height) appeared to be unaffected. Markers of bone turnover in tenofovir disoproxil-treated adolescents suggest increased bone turnover, consistent with the effects observed in adults. Due to the possible effects of tenofovir on bone metabolism, Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate should only be used in adolescents under the age of 18 if the benefits are considered to exceed the risk (see also section 4.8).

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

Osteonecrosis

Osteonecrosis has 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 HIV-negative infants exposed in utero and/or postnatally to nucleoside analogues. The main adverse events reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactataemia, hyperlipasaemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether the neurological disorders are transient or permanent is currently unknown. Any child exposed in utero to nucleoside and nucleotide analogues, even HIV-negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

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, autoimmune hepatitis) 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.

Pancreatitis

Treatment with Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate should be stopped immediately if clinical signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur (see section 4.8).

Effect of food

The administration of Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate 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 be taken on an empty stomach, preferably at bedtime.

Opportunistic infections

Patients receiving antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection. Therefore patients should remain under close clinical observation by a health care providers experienced in the treatment of HIV infection.

Excipients

This medicine contains lactose. Patients with congenital lactase deficiency, galactosaemia or glucose-galactose intolerance must not be given this medicine unless strictly necessary.

The small amount of lactose in each dose is unlikely to cause symptoms of lactose intolerance.

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

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 . 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.

As a fixed combination, Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate should not be administered concomitantly with other medicinal products containing the components, lamivudine or tenofovir disoproxil. Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate should not be co-administered with products containing efavirenz. 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 should not be administered concomitantly with adefovir dipivoxil or with medicinal products containing tenofovir alafenamide.

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).

Concurrent administration with terfenadine, astemizole, cisapride, midazolam, triazolam, pimozide,

bepridil, or ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine) because competition for CYP3A4 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].

Elbasvir/grazoprevir: Co-administration of Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate with elbasvir/grazoprevir is contraindicated because it may lead to loss of virologic response to elbasvir/grazoprevir.

Dasabuvir + ombitasvir/paritaprevir/ritonavir: Co-administration of Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate with dasabuvir + ombitasvir/paritaprevir/ritonavir is contraindicated because it can result in ALT elevations and is expected to reduce the therapeutic effect of dasabuvir + ombitasvir/paritaprevir/ritonavir.

Voriconazole: Co-administration of standard doses of efavirenz and voriconazole is contraindicated.Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate is a fixed-dose combination product, the dose of efavirenz cannot be altered; therefore, voriconazole and Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate must not be co-administered.

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

Sulfamethoxazole/trimethoprim increases plasma concentrations of lamivudine but a clinically significant effect is not expected; the patient should be monitored for lamivudine toxicity in case of marked renal impairment or if high doses of sulfamethoxazole/trimethoprim are used (e.g. for Pneumocystis jirovecii pneumonitis treatment).

Atazanavir/ritonavir

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

Posaconazole

Concomitant use of posaconazole and Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate should be avoided, as this decreases posaconazole plasma concentrations.

Didanosine

Co-administration of Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate and didanosine is not recommended (see section 4.4 and Table 1).

In vitro lamivudine inhibits the intracellular phosphorylation of cladribine leading to a potential risk of cladribine loss of efficacy in case of combination in the clinical setting. Some clinical findings also support a possible interaction between lamivudine and cladribine. Therefore, the concomitant use of lamivudine with cladribine is not recommended (see section 4.4).

Coadministration of sorbitol solution (3.2 g, 10.2 g, 13.4 g) with a single 300 mg dose of lamivudine oral solution resulted in dose-dependent decreases of 14%, 32%, and 36% in lamivudine exposure (AUC∞) and 28%, 52%, and 55% in the Cmax of lamivudine in adults. When possible, chronic coadministration of lamivudine with medicinal products containing sorbitol or other osmotic acting polyalcohols or monosaccharide alcohols (e.g. xylitol, mannitol, lactitol, maltitol) should be avoided. More frequent monitoring of HIV-1 viral load, when chronic coadministration cannot be avoided, should be considered.

Renally eliminated medicinal products

Since lamivudine and tenofovir are primarily eliminated by the kidneys, co-administration of Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate 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 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).

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

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 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		
Emtricitabine /lamivudine		Emtricitabine and Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate should not be co-administered, due to the similarity between emtricitabine and
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
Non-nucleoside inhibitors of reverse transcriptase		
Nevirapine **Etravirine**		Concomitant use not recommended because of additive toxicity and no
Protease inhibitors		
Fosamprenavir/ritonavir (700/100 mg b.i.d)) / efavirenz	amprenavir Ctrough ↓ 17% No significant interaction with twice daily regimen at steady state. Amprenavir	No dose adjustment necessary.
Saquinavir HCG/ritonavir (1000/100 mg 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
Ritonavir (500 mg b.i.d) / efavirenz (600 mg q.d)	Interaction studies have shown moderate increases in the AUC for both ritonavir	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)	Substantial decrease in lopinavir exposure. Lopinavir Cmin ↓ ≈40% Lopinavir concentrations: similar to lopinavir/ritonavir 400/100 mg twice daily without efavirenz Lopinavir/ritonavir: No	Insufficient data are available to make a dosing recommendation for lopinavir/ritonavir when dosed with Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate . Co-administration of lopinavir/ritonavir and Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate is not recommended.
Atazanavir 400 mg / efavirenz	Atazanavir AUCss: ↓ 74% Cmin: ↓ 93%	Concomitant use of Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate and unboosted
Atazanavir (400 mg q.d.)/ tenofovir	Atazanavir: AUC: ↓ 25% Cmax: ↓ 21% Cmin: ↓ 40% Tenofovir: AUC: ↑ 24%	
Atazanavir/ritonavir/Tenofovir disoproxil (300 mg q.d./100 mg q.d./245 mg q.d.)	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-	Co-administration of atazanavir/ritonavir and Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate 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 Cmin	
Tipranavir/ritonavir / efavirenz	Appropriate data on the interaction between the approved	The combination of Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate and
Darunavir/ritonavir (300/100 mg b.i.d) / efavirenz (600 mg q.d) **Darunavir/ritonavir** (300	Darunavir AUCss ↓ 13% Cmax ↓ 15% Cmin ↓ 31%. (CYP3A4 induction) Efavirenz AUC ↑ 21% Cmax ↑ 15% Cmin ↑ 17% (CYP3A4 induction) Darunavir:	HA732 trade name] in combination with darunavir/ritonavir 800/100 mg once daily may result in suboptimal darunavir Cmin. If Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate is to be used in combination with darunavir/ritonavir, the darunavir/ritonavir 600/100 mg twice daily regimen should be used. Darunavir/ritonavir should be used with caution in combination with
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: ↔	Refer to the SmPC for the medicinal product containing maraviroc.
Integrase strand transfer inhibitors		

Raltegravir (400 mg single dose) / efavirenz **Raltegravir** (400 mg b.i.d.) / tenofovir	Raltegravir AUC ↓ 36% Cmax: ↓ 36% (UGT1A1 induction) Raltegravir AUC ↑ 49%	Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate and raltegravir can be co-administered without dose adjustment.
ANTIVIRALS AGAINST HBV		
Adefovir dipivoxil / tenofovir	AUC: ↔ Cmax: ↔	Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate should not be administered concurrently with adefovir dipivoxil
Entecavir (1 mg q.d.)	AUC: ↔ Cmax: ↔	No clinically significant pharmacokinetic interactions when Efavirenz, Lamivudine and
ANTIVIRALS AGAINST HCV		
Elbasvir/grazoprevir (50 mg/200 mg q.d.)/efavirenz	Elbasvir AUC ↓ 54% Cmax↓ 45% C24↓ 59% Grazoprevir AUC ↓ 83% Cmax ↓ 87% C24 ↓ 69%	Concomitant use with Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate is contraindicated
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	The dose of daclatasvir should be increased to 90 mg once daily when coadministered with Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate

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 possibly by	Concomitant use of dasabuvir + ombitasvir/paritaprevir/ritonavir with Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate is contraindicated.
Sofosbuvir / Efavirenz (600 mg q.d.) **Sofosbuvir / Tenofovir**	No clinically significant pharmacokinetic interaction No clinically significant	No dose adjustment required for either medicinal product.
Sofosbuvir/velpatasvir (400 mg/100 mg)	Sofosbuvir AUC: ↔ Cmax: ↑ 20% Velpatasvir ↓	Co-administration of sofosbuvir/velpatasvir with efavirenz resulted in a reduction (approximately 50%) in the systemic exposure of velpatasvir. Co-
Velpatasvir/Sofosbuvir/ Voxilaprevir	Velpatasvir ↓ Expected: Voxilaprevir ↓	Coadministration of sofosbuvir/velpatasvir/voxilaprevir and efavirenz is not recommended because it may result in loss of therapeutic effect of
Ledipasvir (90 mg once daily) / **sofosbuvir** (400 mg once daily) / Efavirenz/ emtricitabine/ tenofovir disoproxil (600 mg/ 200 mg/ 245 mg/ once daily)	Ledipasvir: AUC: ↓ 34% Cmax: ↓ 34% Cmin: ↓ 34% Sofosbuvir: ↔ GS-3310072: ↔ Efavirenz: ↔ Tenofovir: AUC: ↑ 98%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4).
ANTIMYCOBACTERIALS AND ANTIBIOTICS		

Clarithromycin (500 mg b.i.d, multiple doses) / efavirenz	Clarithromycin AUC ↓ 39% Cmax ↓ 26% 14-OH-chlaritromycin AUC ↑ 34% Cmax ↑ 49%	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	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%	Insufficient data are available to make a dosing recommendation for rifampicin in combination with Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate . Therefore co-administration of
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 .
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 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 , these must 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	Possibly increased hepatic toxicity. Co-administration of amodiaquine and Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate should be avoided.

	AUC: ↑114 and 302% respectively.	
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 and Tenofovir Disoproxil fumarate .
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 and Tenofovir Disoproxil fumarate may decrease antimalarial efficacy. When co-treating 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 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% Cmax: ↓44% Proguanil: AUC: ↓43% Cmax: ↔	Concomitant administration of atovaquone/proguanil with Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate 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 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	Co-administration should be avoided unless plasma concentrations of the anticonvulsants and efavirenz can be monitored

	efavirenz.	
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 and valproic acid can be co-administered without dose adjustment.
Vigabatrin, Gabapentin	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.	HA732 trade name] and vigabatrin can be co-administered without dose adjustment.
ANTICOAGULANTS		
Warfarin / efavirenz **Acenocoumarol**/efavirenz	No interaction study available. Co-administration may decrease (and less likely increase) warfarin exposure.	Monitor INR. Dose adjustments of warfarin may be necessary.
ANTIDEPRESSANTS		
Sertraline/efavirenz (50 mg q.d./600 mg q.d.)	Sertraline: AUC: ↓ 39% Cmax: ↓ 29% Cmin: ↓ 46% Efavirenz: AUC: ↔ Cmax: ↑ 11% Cmin: ↔	When co-administered with Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate , sertraline dose increases should be guided by clinical response.

	(CYP3A4 induction)	
Paroxetine/efavirenz (20 mg q.d./600 mg q.d.)	Paroxetine: AUC: ↔ Cmax: ↔ Cmin: ↔ Efavirenz: AUC: ↔ Cmax: ↔ Cmin: ↔	Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate 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 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%	Monitor the clinical effect of diltiazem and increase dose if necessary

	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.	
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 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%	Cholesterol levels should be periodically monitored and the dose of atorvastatin increased in case of insufficient efficacy.

	Total active moiety: AUC: ↓ 34% Cmax: ↓ 20%	
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 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)	A reliable method of barrier contraception should be used in addition to oral contraceptives.

	Norelgestromin AUC □ 64% Cmax: ↓ 46% Cmin: ↓ 82% (active metabolites). Efavirenz : no clinically significant interaction.	
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.
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.
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 .
NON-OPOID ANALGESICS		
Metamizole / efavirenz	Interaction not studied. Decreased exposure of efavirenz may be expected (CYP2B6 and CYP3A4 induction).	Clinical response and/or efavirenz drug levels should be monitored as appropriate.
OPIOIDS		
Methadone / efavirenz (600 mg q.d.)	Methadone AUC ↓ 52% Cmax: ↓ 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	Buprenorphine AUC ↓ 50%;	Despite the decrease in buprenorphine exposure, no

mg q.d.)	norbuprenorphine AUC ↓ 71% Efavirenz : No clinically significant pharmacokinetic interaction.	patients exhibited withdrawal symptoms. Dose adjustment of buprenorphine may not be necessary when co-administered with Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate .

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 Fertility, pregnancy and breastfeeding

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 found no increased risk of overall birth defects in over 2,000 pregnancy outcomes exposed to efavirenz compared with exposure to other antiretroviral drugs. However, risks to the fetus cannot be ruled out. The safety and efficacy of efavirenz 400 mg/day during pregnancy have not been established. 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 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).

As the safety and efficacy of efavirenz 400 mg/day during pregnancy have not been established, the use of Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate during pregnancy is not recommended.

Current recommendations on HIV and pregnancy (e.g. those from the WHO) should be consulted before advising patients on this matter.

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 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.

Severe skin reactions such as Stevens-Johnson syndrome and erythema multiforme, neuropsychiatric adverse reactions (including severe depression, death by suicide, psychosis-like behaviour, seizures); severe hepatic events; pancreatitis and lactic acidosis (sometimes fatal) have been reported.

Rare events of renal impairment, renal failure and proximal renal tubulopathy (including Fanconi syndrome) sometimes leading to bone abnormalities (infrequently contributing to fractures) have also been reported. Monitoring of renal function is recommended for patients receiving Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate (see section 4.4).

The administration of Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate with food may

increase efavirenz exposure and may lead to an increase in the frequency of adverse reactions (see section 5.2).

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).

Metabolic and nutrition disorders

Very common:	hypophosphataemia
Common:	hypertriglyceridaemia
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: *Frequency unknown*	peripheral neuropathy (or paraesthesia)

Psychiatric disorders

Common:	abnormal dreams, anxiety, depression, insomnia
Uncommon:	affect lability, aggression, euphoric mood, hallucination, mania, paranoia, suicide attempt, suicide ideation, psychosis, catatonia
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:	abdominal pain, abdominal distension, flatulence
Uncommon:	pancreatitis, elevated serum amylase

Renal and urinary disorders:

Uncommon:	increased creatinine, proximal renal tubulopathy including Fanconi syndrome proteinuria
Rare:	renal failure (acute and chronic), 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 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 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 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).
Delayed neurotoxicity, sometimes severe, has also been reported in patients receiving efavirenz (see section 4.4) and may require treatment with Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate to be stopped.

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 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
Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (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, autoimmune hepatitis) 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
Paediatric patients

The adverse reactions observed in paediatric patients who received treatment with tenofovir disoproxil or lamivudine as single entities were consistent with those observed in clinical studies in adults.

Reductions in bone mineral density (BMD) have been reported with tenofovir disoproxil in paediatric patients. In HIV-infected adolescents, the BMD Z-scores in subjects who received tenofovir disoproxil were lower than those in subjects who received placebo. In HIV-infected children, the BMD Z-scores in subjects who switched to tenofovir disoproxil were lower than those in subjects who remained on regimens containing stavudine or zidovudine.

Elderly

The combination of efavirenz, lamivudine and tenofovir disoproxil has not been studied in patients over the age of 65. Caution should be exercised since elderly patients are more likely to have decreased renal function.

HIV/HBV or HCV co-infected patients

Clinical studies included only a limited number of patients co-infected with HBV or HCV. The adverse reaction profile of efavirenz, emtricitabine‡ and tenofovir disoproxil in patients co-infected with HIV/HBV or HIV/HCV was similar to that observed in patients infected with HIV without coinfection.

However, as would be expected in this patient population, elevations in AST and ALT occurred more frequently than in the general HIV infected population.

Exacerbations of hepatitis after discontinuation of treatment

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

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

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 via EFDA yellow Card Scheme, online at https://primaryreporting.who-umc.org/ET or toll free call 8482 to Ethiopian food and drug authority (EFDA).

4.9 Overdose

Symptoms

Some patients accidentally taking efavirenz 600 mg twice daily, have reported increased nervous system symptoms. One patient experienced involuntary muscle contractions.
No specific symptoms or signs have been identified following acute overdose with lamivudine, apart from those listed as undesirable effects.
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.
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.
Approximately 10% of the tenofovir dose can be removed by haemodialysis; the median haemodialysis clearance of tenofovir disoproxil is 134 ml/minute. 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: J05AR11

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

Lamivudine, the negative enantiomer of 2'-deoxy-3'-thiacytidine, is a dideoxynucleoside analogue.
Tenofovir disoproxil 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, resulting in DNA chain termination. Both substances are active against HIV-1 and HIV-2, as well as against hepatitis B virus.

The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines including monocytes and PBMCs using standard susceptibility assays. EC 50 values were in the range of 0.003 to 15 microM against HIV-1 clades A-G and group O viruses.

The antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in T lymphoblastoid cell lines, primary monocyte/macrophage cells and PBMCs. The EC50 values for tenofovir were in the range of 0.04-8.5 microM. Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC50 values ranged from 0.5-2.2 microM).

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-retroviral activity (likely through impaired viral fitness). The clinical relevance of these findings is not established.

Cross-resistance conferred by the M184V mutation is limited within the nucleoside/nucleotide inhibitor class of 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 M184V mutation. The M184V mutant shows a <4-fold decrease in susceptibility to didanosine; the clinical significance of this is unknown.

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

been associated with a lack of response to tenofovir-containing regimens. 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 tenofovir 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:

Several clinical studies have confirmed the efficacy of the individual components of this fixed dose combination product. Efavirenz, lamivudine and tenofovir disoproxil were used as single entities in different combination regimens. No clinical studies have been conducted with the combination efavirenz, lamivudine, tenofovir disoproxil.

When tenofovir disoproxil 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 79% and 68% at 48 and 144 weeks, respectively.

No specific studies with the combination efavirenz, lamivudine and tenofovir disoproxil have been conducted in adolescents.

5.2 Pharmacokinetic properties

Absorption of Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate

The absorption characteristics of Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate have been determined after administration of one (1) efavirenz/lamivudine/tenofovir disoproxil fumarate 400 mg / 300 mg / 300 mg tablet in healthy adult volunteers, in the fasted state, as follows:

Pharmacokinetic variable	**Arithmetic mean value (± standard deviation)**		
	Efavirenz	**Lamivudine**	**Tenofovir**
Maximum concentration (Cmax)	1601 ± 473 ng/mL	2086 ± 585 ng/mL	393 ± 125 ng/mL
Area under the curve (AUC0–∞), a measure of the extent of absorption	37785 ± 8985 ng·h/mL*	12143 ± 2726 ng·h/mL	2911 ± 555 ng·h/mL

Time to attain maximum concentration (Tmax)	3.44 ± 1.32 h	2.18 ± 1.13 h	1.11 ± 0.44 h

* AUC0–t

Pharmacokinetics of Efavirenz, Lamivudine and Tenofovir disoproxil

	Efavirenz	**Lamivudine**	**Tenofovir disoproxil**
General **General**	NA	NA	Tenofovir disoproxil is a water-soluble ester prodrug, which is rapidly converted in vivo to tenofovir. Tenofovir is converted intracellularly to tenofovir monophosphate and to the active component, tenofovir diphosphate.
Absorption			
Absolute bioavailability	NA	NA	NA
Oral bioavailability	40% to 45%	80-85%	25% in fasted patients
Food effect	<table><tr><td></td><td>AUC (0-∞)</td><td>Cmax</td></tr><tr><td>High Fat</td><td>28% ↑</td><td>79% ↑</td></tr></table> Food increases absorption	Co-administration of lamivudine with food results in a delay of Tmax and a lower Cmax (decreased by 47%). However, the	<table><tr><td></td><td>AUC (0-∞)</td><td>Cmax</td><td>Tmax</td></tr><tr><td>Light me</td><td>No signif</td><td>No Signi</td><td>No Signif</td></tr></table>

		extent (based on the AUC) of lamivudine absorbed is not influenced.	<table><tr><td>al</td><td>ica nt Eff ect</td><td>fic ant Eff ect</td><td>ica nt eff ect</td></tr><tr><td>Hi gh Fat</td><td>40 % ↑</td><td>14 % ↑</td><td>1 h ↑</td></tr></table> High fat meal increased oral bioavailability
Distribution			
Volume of distribution (mean)	**NA**	After IV admin 1.3 L/kg	800 mL/kg
Plasma proteinbinding *in vitro*	99% (predominantly to albumin)	<36%	< 0.7% (serum protein binding < 7.2%)
Tissue distribution	CSF: mean cerebrospinal fluid concentrations 0.69% of the corresponding plasma concentration for 1 month treatment	mean CSF:serum ratio=0.12. The true extent of penetration or relationship with any clinical efficacy is unknown.	Well distributed, with highest concentrations in kidney and liver.
Metabolism			
	hepatic metabolism metabolised by the cytochrome P450 system to hydroxylated metabolites followed by glucuronidation	Only minor route (< 10%)	*In vitro* studies have determined that neither tenofovir disoproxil nor tenofovir is a substrate for the CYP450 enzymes
Active	None	None	Tenofovir

metabolite(s)			
Elimination			
Elimination half life	52 hrs after single dose and 40 – 55 hrs after multiple doses. Individuals with certain mutant CYP2B6 genotypes have a substantially prolonged terminal half life	5 to 7 hrs lamivudine triphosphate: 16 to 19 hrs in the cell	12 to 18 hrs. Tenofovir diphosphate: 10 hrs in intracellular activated resting peripheral blood mononuclear cells and 50 hrs in resting peripheral blood mononuclear cells
Mean systemic clearance (Cl/F)	NA	Average 0.32 L/h/kg	0.23 L/h/kg
% of dose excreted in urine	14 - 34% recovered in urine and < 1% excreted unchanged	predominantly cleared unchanged by renal excretion.	70-80% as unchanged drug
% of dose excreted in faeces	NA	NA	NA
Pharmacokinetic linearity	In HV, less than dose proportional increase (dose range 100 – 1600 mg). In HIV infected patients, linear steady state pharmacokinetics (dose range 200 – 600 mg/day)	Linear pharmacokinetics	Linear pharmacokinetics (dose range 75 to 600 mg)
Drug interactions *(in vitro*)			
Transporters	**NA**	Substrate for	Substrate of hOAT 1, hOAT3 and

		OCT	MRP 4
Metabolising Enzymes	CYP3A4 and CYP2B6 are the major isoenzymes responsible for efavirenz metabolism. Induces CYP3A4, CYP2B6 and UGT1A1 and possibly CYP2C19 and CYP2C9, although for CYP2C19 and 2C19 also inhibition is observed. Inhibits in vitro CYP3A4.	No CYP3A substrate	No significant inhibition ofCYP3A4, CYP2D6, CYP2C9, CYP2E1, or CYP1A1/2

NA= Not available

Pharmacokinetics in special populations

Age and gender

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) (see section 4.2).

There are no significant or clinically relevant gender differences in the pharmacokinetics of lamivudine and tenofovir. Limited data suggest that females may have higher exposure to efavirenz but they do not appear to be less tolerant of efavirenz.

Ethnicity

There is no evidence that a dose adjustment of efavirenz, tenofovir disoproxil or lamivudine would be required based on the effects of ethnicity on PK parameters.

Renal impairment

The pharmacokinetics of efavirenz have not been studied in patients with renal impairment. However, less than 1% of an efavirenz dose is excreted unchanged in the urine, so the impact of renal impairment on exposure to efavirenz is likely to be minimal.

Pharmacokinetic parameters were determined following administration of single doses of the individual preparations of lamivudine 300 mg or tenofovir disoproxil 245 mg to non-HIV infected patients with varying degrees of renal impairment.

Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate is not recommended for patients with moderate or severe renal impairment (creatinine clearance < 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 4.2 and 4.4).

Hepatic impairment

Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate should be administered with caution to patients with mild hepatic impairment (see sections 4.3 and 4.4).

Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate must not be used in patients with severe hepatic impairment (see section 4.3) and is not recommended for patients with moderate hepatic impairment. In a single-dose study of efavirenz, half-life was doubled in the single patient with severe hepatic impairment (Child-PughTurcotte Class C), indicating a potential for a much greater degree of accumulation. A multiple-dose study of efavirenz showed no significant effect on efavirenz pharmacokinetics in patients with mild hepatic impairment (Child-Pugh-Turcotte Class A) compared with controls. There were insufficient data to determine whether moderate or severe hepatic impairment (Child-Pugh-Turcotte Class B or C) affects efavirenz pharmacokinetics.

The pharmacokinetic parameters of lamivudine were not altered by diminishing hepatic function. Safety and efficacy of lamivudine have not been established in the presence of decompensated liver disease.

The pharmacokinetics of tenofovir following a 245 mg single dose of tenofovir disoproxil have been studied in non-HIV infected subjects with moderate to severe (ChildPugh B to C) hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in subjects with hepatic impairment compared with unimpaired subjects.

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. Based on the totality of the available data 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:

Microcrystalline cellulose, Hydroxypropyl cellulose, Croscarmellose sodium, Ferric oxide yellow, Sodium lauryl sulphate, Purified water, Lactose Monohydrate, Magnesium stearate.

Film-coating:

Macrogol/peg, Polyvinyl alcohol, Talc, Titanium dioxide.

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

With silica gel

30's Count: 100CC HDPE Bottle, 38 mm - 400 ARGUS CR Closure with TEKNIPLEX HS 123 induction sealing wad with Can-sorb-IT 1x3 g silica gel canister.

90's Count: 250CC HDPE Bottle, 53 mm CR Closure with TEKNIPLEX HS 123 induction sealing wad with Can-sorb-IT 1x3 g silica gel canister.

180's Count: 500CC HDPE Bottle, 53 mm - 400 Screw Closure with TEKNIPLEX HS 123 induction sealing wad with Can-sorb-IT 2x3 g silica gel canister.

With molecular sieve

30's Count: 100CC HDPE Bottle, 38 mm - 400 ARGUS CR Closure with TEKNIPLEX HS 123

induction sealing wad with Can tri-sorb 2 x1g Molecular Sieve.

90's Count: White opaque 250 CC HDPE bottles containing CAN TRI-SORB 1 g molecular Sieve 4A closed with 53mm CR closure with TEKNIPLEX HS 123 induction sealing wad with 4X1 g molecular sieve.

180's Count: White opaque 500 CC HDPE bottles containing CAN TRI-SORB 1 g molecular Sieve 4A closed with 53mm- 400 screw closure with TEKNIPLEX HS 123 induction sealing wad with Molecular sieve 6 X 1 g.

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. MARKETING AUTHORIZATION HOLDER

Laurus Labs Limited

2nd Floor, Serene Chambers, Road No.-7

Banjara Hills, Hyderabad – 500034.

India

8. MARKETING AUTHORISATION NUMBER(S)

Certificate No: 08746/08335/VAR/2023

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Jun 8, 2023

10. DATE OF REVISION OF THE TEXT

September 2023