APPROVED PACKAGE INSERT – 6 JUNE 2012

SCHEDULING STATUS: S4

PROPRIETARY NAMES (AND DOSAGE FORM):

EFLATEN (film-coated tablets)

COMPOSITION:

Each film-coated tablet contains:

Tenofovir disoproxil fumarate	300 mg
Lamivudine	300 mg
Efavirenz	600 mg

List of Excipients:

Microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, sodium lauryl sulfate, sodium chloride, magnesium stearate, lactose monohydrate, film coat {titanium dioxide, macrogol, talc}

WARNING:

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION WITH OTHER ANTIRETROVIRALS (SEE WARNINGS).

TENOFOVIR AS CONTAINED IN EFLATEN IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION. SAFETY AND EFFICACY OF TENOFOVIR HAS NOT BEEN ESTABLISHED IN PATIENTS CO-INFECTED WITH HBV AND HIV. SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO ARE CO-INFECTED WITH HBV AND HIV AND HAVE DISCONTINUED TENOFOVIR. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE TENOFOVIR AND ARE CO-INFECTED WITH HIV AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS).

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.8 Antiviral agents.

PHARMACOLOGICAL ACTION:

Tenofovir Disoproxil Fumarate

Mechanism of action:

Tenofovir disoproxil fumarate is the fumarate salt of the prodrug tenofovir disoproxil. Tenofovir disoproxil is absorbed and converted to the active substance tenofovir, which is a nucleoside monophosphate (nucleotide) analogue. Tenofovir is then converted to the active metabolite, tenofovir diphosphate, by constitutively expressed cellular enzymes through two phosphorylation reactions in both resting and activated T cells. Tenofovir diphosphate has an intracellular half-life of 10 hours in activated and 50 hours in resting peripheral blood mononuclear cells (PBMCs).

Tenofovir diphosphate inhibits viral polymerases by direct binding competition with the natural deoxyribonucleotide substrate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of cellular polymerases α, β, and γ, with kinetic inhibition constants (Ki) that are > 200-fold higher against human DNA polymerase α (5,2 µmol/l) and > 3,000-fold higher against human DNA polymerase β and γ (81,7 and 59,5 µmol/l, respectively) than its Ki against HIV-1 reverse transcriptase (0,02 µmol/l). At concentrations of up to 300 µmol/l, tenofovir has also shown no effect on the synthesis of mitochondrial DNA or the production of lactic acid in *in vitro* assays.

Pharmacodynamic effects:

Tenofovir has *in vitro* antiviral activity against retroviruses and hepadnaviruses.

The concentration of tenofovir required for 50 % inhibition (IC_{50}) of the wild-type laboratory strain HIV-1IIIB is 1-6 µmol/l in lymphoid cell lines and 1,1 µmol/l against primary HIV-1 subtype B isolates in PBMCs. Tenofovir is also active against HIV-1 subtypes A, C, D, E, F, G, and O and against HIVBaL in primary monocyte/macrophage cells. Tenofovir shows activity in vitro against HIV-2, with an IC_{50} of 4,9 µmol/l in MT-4 cells and against hepatitis B virus, with an IC_{50} of 1,1 µmol/l in HepG2 2.2.15 cells.

The activity of tenofovir remains within twofold of wild-type IC_{50} against recombinant HIV-1 expressing didanosine resistance (L74V), zalcitabine resistance (T69D), and multinucleoside drug resistance (Q151M complex) mutations. The activity of tenofovir against HIV-1 strains with zidovudine-associated mutations appears to depend on the type and number of these resistance mutations. In the presence of mutation T215Y, a

twofold increase of the IC_{50} was observed. In 10 samples which had multiple zidovudine-associated mutations (mean 3,4), a mean 3,7-fold increase of the IC_{50} was observed (range 0,8 to 8,4).

Multinucleoside resistant HIV-1 with T69S double insertions has reduced susceptibility to tenofovir (IC_{50} > 10-fold). Tenofovir shows full activity against non-nucleoside reverse transcriptase inhibitor resistant HIV-1 with K103N or Y181C mutations. Cross-resistance to protease inhibitor resistance mutations is not expected due to the different viral enzymes targeted.

Strains of HIV-1 with 3- to 4-fold reduced susceptibility to tenofovir and a K65R mutation in reverse transcriptase have been selected *in vitro*. The K65R mutation in reverse transcriptase can also be selected by zalcitabine, didanosine, and abacavir, and causes reduced susceptibility to zalcitabine, didanosine, abacavir, and lamivudine (14-, 4-,3-, and 25-fold, respectively). Tenofovir disoproxil fumarate should be avoided in antiretroviral experienced patients with strains harbouring the K65R mutation.

The clinical activity of tenofovir disoproxil fumarate has not been determined against hepatitis B virus (HBV) in humans. It is unknown whether treatment of patients co-infected with HIV-1 and HBV will result in the development of HBV resistance to tenofovir disoproxil fumarate or other medicinal products.

Lamivudine

Lamivudine is a nucleoside analogue which has activity against human immunodeficiency virus (HIV) and hepatitis B virus (HBV). It is metabolised intracellularly to the active moiety, lamivudine 5'-triphosphate. Its main mode of action is

as a chain terminator of viral reverse transcription. The triphosphate has selective inhibitory activity against HIV-1 and HIV-2 replication *in vitro*; it is also active against zidovudine-resistant clinical isolates of HIV. Lamivudine in combination with zidovudine exhibits synergistic anti-HIV activity against clinical isolates in cell culture.

HIV-1 resistance to lamivudine involves the development of a M184V amino acid change close to the active site of the viral reverse transcriptase (RT). This variant arises both *in vitro* and in HIV-1 infected patients treated with lamivudine-containing antiretroviral therapy. M184V mutants display greatly reduced susceptibility to lamivudine and show diminished viral replicative capacity *in vitro*. *In vitro* studies indicate that zidovudine-resistant virus isolates can become zidovudine sensitive when they simultaneously acquire resistance to lamivudine. The clinical relevance of such findings remains, however, not well defined.

Cross-resistance conferred by the M184V RT is limited within the nucleoside inhibitor class of antiretroviral agents. 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 RT mutant shows a <4-fold decrease in susceptibility to didanosine and zalcitabine; the clinical significance of these findings is unknown. *In vitro* susceptibility testing has not been standardized and results may vary according to methodological factors.

Lamivudine demonstrates low cytotoxicity to peripheral blood lymphocytes, to established lymphocyte and monocyte-macrophage cell lines, and to a variety of bone marrow progenitor cells *in vitro*.

Efavirenz

Mechanism of action:

Efavirenz is a NNRTI of HIV-1. Efavirenz is a non-competitive inhibitor of HIV-1 reverse transcriptase (RT) and does not significantly inhibit HIV-2 RT or cellular DNA polymerases (α, β, γ or δ).

Antiviral activity:

The free concentration of efavirenz required for 90 to 95 % inhibition of wild type or zidovudine resistant laboratory and clinical isolates in vitro ranged from 0,46 to 6,8 nM in lymphoblastoid cell lines, peripheral blood mononuclear cells (PBMCs) and macrophage/monocyte cultures.

Resistance:

The potency of efavirenz in cell culture against viral variants with amino acid substitutions at positions 48, 108, 179, 181 or 236 in RT or variants with amino acid substitutions in the protease was similar to that observed against wild type viral strains. The single substitutions which led to the highest resistance to efavirenz in cell culture correspond to a leucine to isoleucine change at position 100 (L100I, 17 to 22-fold resistance) and a lysine-to-asparagine at position 103 (K103N, 18 to 33-fold resistance). Greater than 100-fold loss of susceptibility was observed against HIV variants expressing K103N in addition to other amino acid substitutions in RT.

K103N was the most frequently observed RT substitution in viral isolates from patients who experienced a significant rebound in viral load during clinical studies of efavirenz in combination with indinavir or zidovudine + lamivudine. This mutation was observed in

90 % of patients receiving efavirenz with virological failure. Substitutions at RT positions 98, 100, 101, 108, 138, 188, 190 or 225 were also observed, but at lower frequencies, and often only in combination with K103N. The pattern of amino acid substitutions in RT associated with resistance to efavirenz was independent of the other antiviral medications used in combination with efavirenz.

Cross resistance:

Cross resistance profiles for efavirenz, nevirapine and delavirdine in cell culture demonstrated that the K103N substitution confers loss of susceptibility to all three NNRTIs. Two of three delavirdine-resistant clinical isolates examined were cross-resistant to efavirenz and contained the K103N substitution. A third isolate which carried a substitution at position 236 of RT was not cross-resistant to efavirenz.

Viral isolates recovered from PBMCs of patients enrolled in efavirenz clinical studies who showed evidence of treatment failure (viral load rebound) were assessed for susceptibility to NNRTIs. Thirteen isolates previously characterised as efavirenz-resistant were also resistant to nevirapine and delavirdine. Five of these NNRTI-resistant isolates were found to have K103N or a valine-to-isoleucine substitution at position 108 (V108I) in RT. Three of the efavirenz treatment failure isolates tested remained sensitive to efavirenz in cell culture and were also sensitive to nevirapine and delavirdine.

The potential for cross resistance between efavirenz and PIs is low because of the different enzyme targets involved. The potential for cross-resistance between efavirenz and NRTIs is low because of the different binding sites on the target and mechanism of action.

Pharmacodynamic effects

Efavirenz has not been studied in controlled studies in patients with advanced HIV disease, namely with CD4 counts < 50 cells/mm^3, or in PI or NNRTI experienced patients. Clinical experience in controlled studies with combinations including didanosine or zalcitabine is limited.

Pharmacokinetic properties:

Tenofovir disoproxil fumarate:

Tenofovir disoproxil fumarate is a water soluble ester prodrug which is rapidly converted *in vivo* to tenofovir and formaldehyde.

Tenofovir is converted intracellularly to tenofovir monophosphate and to the active component, tenofovir diphosphate.

Absorption:

Following oral administration of tenofovir disoproxil fumarate to HIV infected patients, tenofovir disoproxil fumarate is rapidly absorbed and converted to tenofovir. Administration of multiple doses of tenofovir disoproxil fumarate with a meal to HIV infected patients resulted in mean (%CV) tenofovir C_{max}, $AUC_{0-\infty}$, and C_{min} values of 326 (36,6 %) ng/ml, 3,324 (41,2 %) ng·hr/ml and 64,4 (39,4 %) ng/ml, respectively. Maximum tenofovir concentrations are observed in serum within one hour of dosing in the fasted state and within two hours when taken with food. The oral bioavailability of tenofovir from tenofovir disoproxil fumarate in fasted patients was approximately 25 %. Administration of tenofovir disoproxil fumarate with a high fat meal enhanced the oral bioavailability, with an increase in tenofovir AUC by approximately 40 % and C_{max} by

approximately 14 %. Following the first dose of tenofovir disoproxil fumarate in fed patients, the median C_{max} in serum ranged from 213 to 375 ng/ml. However, aministration of tenofovir disoproxil fumarate with a light meal did not have a significant effect on the pharmacokinetics of tenofovir.

Distribution:

Following intravenous administration the steady-state volume of distribution of tenofovir was estimated to be approximately 800 ml/kg. After oral administration of tenofovir disoproxil fumarate, tenofovir is distributed to most tissues with the highest concentrations occurring in the kidney, liver and the intestinal contents (preclinical studies). *In vitro* protein binding of tenofovir to plasma or serum protein was less than 0,7 and 7,2 %, respectively, over the tenofovir concentration range 0,01 to 25 µg/ml.

Biotransformation:

In vitro studies have determined that neither tenofovir disoproxil fumarate nor tenofovir are substrates for the CYP450 enzymes. Moreover, at concentrations substantially higher (approximately 300-fold) than those observed *in vivo*, tenofovir did not inhibit *in vitro* drug metabolism mediated by any of the major human CYP450 isoforms involved in drug biotransformation (CYP3A4, CYP2D6, CYP2C9, CYP2E1, or CYP1A1/2). Tenofovir disoproxil fumarate at a concentration of 100 µmol/l had no effect on any of the CYP450 isoforms, except CYP1A1/2, where a small (6 %) but statistically significant reduction in metabolism of CYP1A1/2 substrate was observed. Based on these data, it is unlikely that clinically significant interactions involving tenofovir disoproxil fumarate and medicinal products metabolised by CYP450 would occur.

Elimination:

Tenofovir is primarily excreted by the kidney by both filtration and an active tubular transport system with approximately 70-80 % of the dose excreted unchanged in urine following intravenous administration. Total clearance has been estimated to be approximately 230 ml/h/kg (approximately 300 ml/min). Renal clearance has been estimated to be approximately 160 ml/h/kg (approximately 210 ml/min), which is in excess of the glomerular filtration rate. This indicates that active tubular secretion is an important part of the elimination of tenofovir. Following oral administration the terminal half-life of tenofovir is approximately 12 to 18 hours.

Age and gender:

Limited data on the pharmacokinetics of tenofovir in women indicate no major gender effect.

Pharmacokinetic studies have not been performed in children and adolescents (under 18) or in the elderly (over 65).

Pharmacokinetics has not been specifically studied in different ethnic groups.

Renal impairment:

Pharmacokinetic parameters of tenofovir were determined following administration of a single dose of tenofovir disoproxil 245 mg to 40 non-HIV infected patients with varying degrees of renal impairment defined according to baseline creatinine clearance (CrCl) (normal renal function when CrCl> 80 ml/min; mild with CrCl = 50-79 ml/min; moderate with CrCl = 30-49 ml/min and severe with CrCl = 10-29 ml/min). Compared with patients with normal renal function, the mean (%CV) tenofovir exposure increased from 2,185 (12 %) ng·h/ml in subjects with CrCl> 80 ml/min to respectively 3,064 (30 %) ng·h/ml, 6,009 (42 %) ng·h/ml and 15,985 (45 %) ng·h/ml in patients with mild, moderate and severe

renal impairment. The dosing recommendations in patients with renal impairment, with increased dosing interval, are expected to result in higher peak plasma concentrations and lower C_{min} levels in patients with renal impairment compared with patients with normal renal function. The clinical implications of this are unknown.

In patients with end-stage renal disease (ESRD) (CrCl < 10 ml/min) requiring haemodialysis, between dialysis tenofovir concentrations substantially increased over 48 hours achieving a mean C_{max} of 1,032 ng/ml and a mean AUC_{0-48h} of 42,857 ng·h/ml.

It is recommended that the dosing interval for tenofovir disoproxil 245 mg (as fumarate) is modified in patients with creatinine clearance < 50 ml/min or in patients who already have ESRD and require dialysis.

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

Hepatic Impairment:

A single 245 mg dose of tenofovir disoproxil was administered to non-HIV infected patients with varying degrees of hepatic impairment defined according to Child-Pugh-Turcotte (CPT) classification. Tenofovir pharmacokinetics were not substantially altered in subjects with hepatic impairment suggesting that no dose adjustment is required in these subjects. The mean (%CV) tenofovir C_{max} and $AUC_{0-\infty}$ values were 223 (34,8 %) ng/ml and 2,050 (50,8 %) ng·h/ml, respectively, in normal subjects compared with 289 (46,0 %) ng/ml and 2,310 (43,5 %) ng·h/ml in subjects with moderate hepatic

impairment, and 305 (24,8 %) ng/ml and 2,740 (44,0 %) ng·h/ml in subjects with severe hepatic impairment.

Intracellular pharmacokinetics:

In non-proliferating human peripheral blood mononuclear cells (PBMCs) the half-life of tenofovir diphosphate was found to be approximately 50 hours, whereas the half-life in phytohaemagglutinin-stimulated PBMCs was found to be approximately 10 hours.

Lamivudine:

Absorption:

Lamivudine is well absorbed from the gastrointestinal tract, and the bioavailability of oral lamivudine in adults is normally between 80 and 85 %. Following oral administration, the mean time (t_{max}) to maximal serum concentrations (C_{max}) is about an hour. Based on data derived from a study in healthy volunteers, at a therapeutic dose of 150mg twice daily, mean (CV) steady-state C_{max} and C_{min} of lamivudine in plasma are 1,2 µg/ml (24 %) and 0,09 µg/ml (27 %), respectively. The mean (CV) AUC over a dosing interval of 12 hours is 4,7 µg.h/ml (18 %). At a therapeutic dose of 300 mg once daily, the mean (CV) steady-state C_{max}, C_{min} and 24h AUC are 2,0 µg/ml (26 %), 0,04 µg/ml (34 %) and 8,9 µg.h/ml (21 %), respectively.

The 150 mg tablet is bioequivalent and dose proportional to the 300 mg tablet with respect to AUC_{∞}, C_{max}, and t_{max}.

Co-administration of lamivudine with food results in a delay of t_{max} and a lower C_{max} (decreased by 47 %). However, the extent (based on the AUC) of lamivudine absorbed is not influenced.

Distribution:

From intravenous studies, the mean volume of distribution is 1,3 l/kg. The observed 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 %) via the organic cationic transport system.

Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited binding to the major plasma protein albumin (< 16 % - 36 % to serum albumin in *in vitro* studies).

Limited data show that lamivudine penetrates the central nervous system and reaches the cerebro-spinal fluid (CSF). The mean ratio CSF/serum lamivudine concentration 2-4 hours after oral administration was approximately 0,12. The true extent of penetration or relationship with any clinical efficacy is unknown.

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}.

Lamivudine is predominately cleared unchanged by renal excretion. The likelihood of metabolic interactions of lamivudine with other medicinal products is low due to the small extent of hepatic metabolism (5-10 %) and low plasma protein binding.

Elimination: Studies in patients with renal impairment show lamivudine elimination is affected by renal dysfunction.

Pharmacokinetics in children:

In general, lamivudine pharmacokinetics in pediatric patients is similar to adults. However, absolute bioavailability (approximately 55-65 %) was reduced in pediatric patients below 12 years of age. In addition, systemic clearance values were greater in younger pediatric patients and decreased with age, approaching adult values around 12 years of age. Due to these differences, the recommended dose for children from three months to 12 years is 8 mg/kg/day, which will achieve similar adult and pediatric exposure (average AUC approximately 5,000 ng.h/ml).

There are limited pharmacokinetic data for patients less than three months of age. In neonates one week of age, lamivudine oral clearance was reduced when compared to pediatric patients and is likely to be due to immature renal function and variable absorption. Therefore to achieve similar adult and pediatric exposure, the recommended dose for neonates is 4 mg/kg/day. Glomerular filtration estimates suggests that to achieve similar adult and pediatric exposure, the recommended dose for children aged six weeks and older could be 8 mg/kg/day.

Pharmacokinetics in pregnancy:

Following oral administration, lamivudine pharmacokinetics in late-pregnancy were similar to non-pregnant women.

Efavirenz

Absorption

Peak efavirenz plasma concentrations of 1,6 to 9,1 µM were attained by 5 hours following single oral doses of 100 mg to 1,600 mg administered to uninfected volunteers. Dose related increases in C_{max} and AUC were seen for doses up to 1,600 mg; the increases were less than proportional suggesting diminished absorption at higher doses. Time to peak plasma concentrations (3-5 hours) did not change following multiple dosing and steady-state plasma concentrations were reached in 6-7 days.

In HIV infected patients at steady state, mean C_{max}, mean C_{min}, and mean AUC were linear with 200 mg, 400 mg, and 600 mg daily doses. In 35 patients receiving efavirenz 600 mg once daily, steady state C_{max} was 12,9 ± 3,7 µM (29 %) [Mean ± S.D. (% C.V.)], steady state C_{min} was 5,6 ± 3,2 µM (57 %), and AUC was 184 ± 73 µM·h (40 %).

Effect of food

The AUC and C_{max} of a single 600 mg dose of efavirenz film‑coated tablets in uninfected volunteers was increased by 28 % (90 % CI: 22-33 %) and 79 % (90 % CI: 58-102 %), respectively, when given with a high fat meal, relative to when given under fasted conditions.

Distribution

Efavirenz is highly bound (approximately 99,5-99,75 %) to human plasma proteins, predominantly albumin. In HIV-1 infected patients (n = 9) who received efavirenz 200 to 600 mg once daily for at least one month, cerebrospinal fluid concentrations ranged from 0,26 to 1,19 % (mean 0,69 %) of the corresponding plasma concentration. This proportion is approximately 3-fold higher than the non-protein-bound (free) fraction of efavirenz in plasma.

Biotransformation

Studies in humans and in vitro studies using human liver microsomes have demonstrated that efavirenz is principally metabolised by the cytochrome P450 system to hydroxylated metabolites with subsequent glucuronidation of these hydroxylated metabolites. These metabolites are essentially inactive against HIV-1. The in vitro studies suggest that CYP3A4 and CYP2B6 are the major isozymes responsible for efavirenz metabolism and that it inhibited P450 isozymes 2C9, 2C19, and 3A4. In in vitro studies efavirenz did not inhibit CYP2E1 and inhibited CYP2D6 and CYP1A2 only at concentrations well above those achieved clinically.

Efavirenz has been shown to induce P450 enzymes, resulting in the induction of its own metabolism. In uninfected volunteers, multiple doses of 200-400 mg per day for 10 days resulted in a lower than predicted extent of accumulation (22 - 42 % lower) and a shorter terminal half-life of 40-55 hours (single dose half-life 52-76 hours).

Elimination

Efavirenz has a relatively long terminal half-life of 52 to 76 hours after single doses and 40-55 hours after multiple doses. Approximately 14-34 % of a radiolabelled dose of efavirenz was recovered in the urine and less than 1 % of the dose was excreted in urine as unchanged efavirenz.

In the single patient studied with severe hepatic impairment (Child Pugh Grade C), half life was doubled indicating a potential for a much greater degree of accumulation.

Gender, race, elderly

Although limited data suggest that Asian and Pacific Island patients may have higher exposure to efavirenz, they do not appear to be less tolerant of efavirenz. Pharmacokinetic studies have not been performed in the elderly.

INDICATIONS:

EFLATEN is indicated for the treatment of HIV-1 infected adults over 18 years of age, who have been treated and stabilised on a combination of the 3 (three) antiretrovirals contained in **EFLATEN** administered as separate formulations in similar dosages as contained in **EFLATEN**.

CONTRA-INDICATIONS:

- Severe hepatic impairment (Child-Pugh Class C)
- Severe renal impairment
- Pregnancy and lactation
- Concurrent administration with astemizole, cisapride, midazolam, triazolam, pimozide, bepridil, ergot alkaloids, St John's wort (hypericum perforatum) or zalcitabine.

EFLATEN Tablets are contra-indicated in patients with known hypersensitivity to tenofovir or lamivudine or efavirenz.

WARNINGS:

EFLATEN should not be taken with any other medicinal products containing tenofovir disoproxil fumarate or lamivudine.

Tenofovir disoproxil fumarate

Tenofovir disoproxil fumarate has not been studied in patients under the age of 18.

Tenofovir is principally eliminated via the kidney. Tenofovir exposure may be markedly increased in patients with moderate or severe renal impairment (creatinine clearance <

50 ml/min) receiving daily doses of tenofovir disoproxil 245 mg (as fumarate). Consequently, a dosing interval adjustment is required in all patients with creatinine clearance < 50 ml/min. Careful monitoring for signs of toxicity, such as deterioration of renal function, but also for changes in viral load is required in patients with pre-existing renal impairment once Tenofovir disoproxil fumarate has been started at prolonged dosing intervals. The safety and efficacy of Tenofovir disoproxil fumarate in patients with renal impairment have not been established.

Renal impairment, which may include hypophosphataemia, has been reported with the use of tenofovir disoproxil fumarate.

Monitoring of renal function (creatinine clearance and serum phosphate) is recommended before taking tenofovir disoproxil fumarate, every four weeks during the first year, and then every three months. In patients at risk for, or with a history of, renal dysfunction, and patients with renal insufficiency, consideration should be given to more frequent monitoring of renal function.

Tenofovir disoproxil fumarate has not been evaluated in patients receiving nephrotoxic medicinal products (e.g. aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2). Use of tenofovir disoproxil fumarate should be avoided with concurrent or recent use of a nephrotoxic medicinal product. If concomitant use of tenofovir disoproxil fumarate and nephrotoxic agents is unavoidable, renal function should be monitored weekly.

Tenofovir disoproxil fumarate has not been clinically evaluated in patients receiving medicinal products which are secreted by the same renal transporter, human organic

anion transporter 1 (hOAT1) (e.g. adefovir dipivoxil; cidofovir, a known nephrotoxic medicinal product).

Tenofovir disoproxil fumarate should be avoided in antiretroviral experienced patients with strains harbouring the K65R mutation.

Tenofovir disoproxil fumarate has not been studied in patients over the age of 65. Elderly patients are more likely to have decreased renal function; therefore caution should be exercised when treating elderly patients with tenofovir disoproxil fumarate.

Liver disease:

Tenofovir and tenofovir disoproxil fumarate are not metabolized by liver enzymes. A pharmacokinetic study has been performed in non-HIV infected patients with various degrees of hepatic impairment. No significant pharmacokinetic alteration has been observed in these patients.

The safety and efficacy data of tenofovir disoproxil fumarate are limited in patients with significant underlying liver disorders. 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 events. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy 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.

Lactic acidosis:

Lactic acidosis, usually associated with hepatic steatosis, has been reported with the use of nucleoside analogues. The preclinical and clinical data suggest that the risk of occurrence of lactic acidosis, a class effect of nucleoside analogues, is low for tenofovir disoproxil fumarate. However, as tenofovir is structurally related to nucleoside analogues, this risk cannot be excluded. Early symptoms (symptomatic hyperlactatemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non-specific malaise, and loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness). Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure or renal failure. Lactic acidosis generally occurred after a few or several months of treatment.

Treatment with nucleoside analogues should be discontinued in the setting of symptomatic hyperlactatemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.

Caution should be exercised when administering nucleoside analogues to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicinal products and alcohol). Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk.

Patients at increased risk should be followed closely.

Immune Reactivation Syndrome:

In HIV infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterium infections, and *Pneumocystis carinii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Co-administration of tenofovir disoproxil fumarate and didanosine results in a 40-60 % increase in systemic exposure to didanosine that may increase the risk for didanosine-related adverse events. Rare cases of pancreatitis and lactic acidosis, sometimes fatal, have been reported.

Triple nucleoside therapy:

There have been reports of a high rate of virological failure and of emergence of resistance at early stage when tenofovir disoproxil fumarate was combined with lamivudine and abacavir as well as with lamivudine and didanosine as a once daily regimen.

Patients must be advised that antiretroviral therapies, including tenofovir disoproxil fumarate, have not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions must continue to be used.

Lamivudine: *Renal impairment:*

In patients with moderate to severe renal impairment, the terminal plasma half-life of lamivudine is increased due to decreased clearance; therefore the dose should be adjusted.

Triple nucleoside therapy:

There have been reports of a high rate of virological failure and of emergence of resistance at an early stage when lamivudine was combined with tenofovir disoproxil fumarate and Abacavir as well as with tenofovir disoproxil fumarate and didanosine as a once daily regimen.

Opportunistic infections:

Patients receiving Lamivudine or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with associated HIV diseases.

Transmission of HIV:

Patients should be advised that current antiretroviral therapy, including Lamivudine, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or contamination with blood. Appropriate precautions should continue to be taken.

Pancreatitis:

Cases of pancreatitis have occurred rarely. Treatment with Lamivudine should be stopped immediately if clinical signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur.

***Lactic acidosis*:**

Lactic acidosis, usually associated with hepatomegaly and hepatic steatosis, has been reported with the use of nucleoside analogues.

Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure, or renal failure.

Lactic acidosis generally occurred after a few or several months of treatment.

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 post-natally to nucleoside analogues. The main adverse events reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactatemia, hyperlipasemia). 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.

Lipodystrophy:

Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown.

Immune Reactivation Syndrome:

In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms.

***Liver disease*:**

If lamivudine is being used concomitantly for the treatment of HIV and HBV, additional information relating to the use of lamivudine in the treatment of hepatitis B infection is available in the Zeffix SPC.

Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk of severe and potentially fatal hepatic adverse events. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

Osteonecrosis:

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

Efavirenz

Rash:

Mild to moderate rash has been reported in clinical studies with efavirenz and usually resolves with continued therapy. Appropriate antihistamines and/or corticosteroids may improve the 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. The incidence of erythema multiforme or Stevens-Johnson syndrome was approximately 0,1 %. Efavirenz must be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. If therapy with efavirenz is discontinued, consideration should also be given to interrupting therapy with other antiretroviral agents to avoid development of resistant virus.

Rash was reported in 26 of 57 children (46 %) treated with efavirenz during a 48-week period and was severe in three patients. Prophylaxis with appropriate antihistamines prior to initiating therapy with efavirenz in children may be considered.

Patients who discontinued treatment with other NNRTIs due to rash may be at higher risk of developing rash during treatment with efavirenz.

Psychiatric symptoms:

Psychiatric adverse experiences have been reported in patients treated with efavirenz. Patients with a prior history of psychiatric disorders appear to be at greater risk of these serious psychiatric adverse experiences. 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 behaviour. 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 risks of continued therapy outweigh the benefits.

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. Nervous system symptoms usually begin during the first one or two days of therapy and generally resolve after the first 2 to 4 weeks. Patients should be informed that if they do occur, these common symptoms are likely to improve with continued therapy and are not predictive of subsequent onset of any of the less frequent psychiatric symptoms.

Seizures:

Convulsions have been observed rarely in patients receiving efavirenz, generally in the presence of known medical history of seizures. Patients who are receiving concomitant anticonvulsant medicinal products primarily metabolised 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. Caution must be taken in any patient with a history of seizures.

Effect of food:

The administration of Efavirenz with food may increase efavirenz exposure and may lead to an increase in the frequency of undesirable effects. This effect may be more evident for the film-coated tablets than for the hard capsules. It is recommended that Efavirenz be taken on an empty stomach, preferably at bedtime.

Immune Reactivation Syndrome:

In HIV infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis carinii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Lipodystrophy and metabolic abnormalities:

Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long‑term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and PIs and lipoatrophy and NRTIs has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include

evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

Osteonecrosis:

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

INTERACTIONS:

Tenofovir disoproxil fumarate:

Based on the results of *in vitro* experiments and the known elimination pathway of tenofovir, the potential for CYP450 mediated interactions involving tenofovir with other medicinal products is low.

Tenofovir is excreted renally, both by filtration and active secretion via the anionic transporter (hOAT1). Co-administration of tenofovir disoproxil fumarate with other medicinal products that are also actively secreted via the anionic transporter (e.g. cidofovir) may result in increased concentrations of tenofovir or of the co-administered medicinal product.

Concomitant antiretroviral medicinal products:

Emtricitabine, lamivudine, indinavir, efavirenz, nelfinavir, and saquinavir (ritonavir boosted): Co-administration with tenofovir disoproxil fumarate did not result in any clinically relevant interaction.

When tenofovir disoproxil fumarate was administered with lopinavir/ritonavir, no changes were observed in the pharmacokinetics of lopinavir and ritonavir. Tenofovir AUC was increased by approximately 30 % when tenofovir disoproxil fumarate was administered with lopinavir/ritonavir.

Other interactions:

Co-administration of tenofovir disoproxil fumarate, methadone, ribavirin, adefovir dipivoxil or the hormonal contraceptive norgestimate/ethinyl oestradiol did not result in any pharmacokinetic interaction.

Tenofovir disoproxil fumarate must be taken with food, as food enhances the bioavailability of Tenofovir.

Co-administration of zidovudine results in a 13 % increase in zidovudine exposure and a 28 % increase in peak plasma levels. This is not considered to be of significance to patient safety and therefore no dosage adjustments are necessary.

Lamivudine:

Interaction studies have only been performed in adults.

An interaction with trimethoprim, a constituent of co-trimoxazole, causes a 40 % increase in lamivudine exposure at therapeutic doses. This does not require dose adjustment unless the patient also has renal impairment. Administration of co-trimoxazole with lamivudine in patients with renal impairment should be carefully assessed.

Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicinal products are used concurrently. Lamivudine is therefore not recommended to be used in combination with zalcitabine.

Co-administration of lamivudine with intravenous ganciclovir or foscarnet is not recommended.

The likelihood of metabolic interactions is low due to limited metabolism and plasma protein binding and almost complete renal clearance.

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. 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 carinii* pneumonia (PCP) and toxoplasmosis should be avoided.

The possibility of interactions with other medicinal products administered concurrently should be considered, particularly when the main route of elimination is active renal secretion via the organic cationic transport system e.g. trimethoprim. Other medicinal products (e.g. ranitidine, cimetidine) are eliminated only in part by this mechanism and were shown not to interact with lamivudine. The nucleoside analogues (e.g. didanosine and zalcitabine) like zidovudine are not eliminated by this mechanism and are unlikely to interact with lamivudine.

A modest increase in C_{max} (28 %) was observed for zidovudine when administered with lamivudine, however overall exposure (AUC) is not significantly altered. Zidovudine has no effect on the pharmacokinetics of lamivudine.

Lamivudine metabolism does not involve CYP3A, making interactions with medicinal products metabolized by this system (e.g. PIs) unlikely.

Efavirenz

Efavirenz is an inducer of CYP3A4 and an inhibitor of some CYP isozymes including CYP3A4. Other compounds that are substrates of CYP3A4 may have decreased plasma concentrations when coadministered with efavirenz. Efavirenz exposure may also be altered when given with medicinal products or food (for example, grapefruit juice) which affect CYP3A4 activity.

Efavirenz 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.

Concomitant antiretroviral agents

Protease Inhibitors:

Amprenavir:

No dosage adjustment is necessary if efavirenz is given in combination with amprenavir (600 mg twice daily) and ritonavir (100 or 200 mg twice daily).

Further, if efavirenz is given in combination with amprenavir and nelfinavir, no dosage adjustment is necessary for any of the medicinal products. Treatment with efavirenz in combination with amprenavir and saquinavir is not recommended, as the exposure to both PIs is expected to be significantly decreased. No dose recommendation can be given for the co administration of amprenavir with another PI and efavirenz in children and patients with renal impairment. Such combinations should be avoided in patients with hepatic impairment.

Atazanavir:

Co-administration of efavirenz and atazanavir in combination with ritonavir may lead to increases in efavirenz exposure which may worsen the tolerability profile of efavirenz. Co-administration of efavirenz 600 mg with atazanavir in combination with low-dose ritonavir resulted in substantial decreases in atazanavir exposure, necessitating dosage adjustment of atazanavir.

Indinavir:

No adjustment of the dose of efavirenz is necessary when given with indinavir or indinavir/ritonavir.

Lopinavir/ritonavir:

When co‑administered with efavirenz, an increase of the lopinavir/ritonavir doses by 33 % should be considered (4 capsules/~6,5 ml twice daily instead of 3 capsules/5 ml twice daily). Caution is warranted since this dosage adjustment might be insufficient in some patients.

Nelfinavir:

No dose adjustment is necessary when nelfinavir is administered in combination with efavirenz.

Ritonavir:

When efavirenz was given with ritonavir 500 mg or 600 mg twice daily, the combination was not well tolerated (for example, dizziness, nausea, paraesthesia and elevated liver enzymes occurred).

Saquinavir:

Use of efavirenz in combination with saquinavir as the sole PI is not recommended.

Saquinavir/ritonavir:

No data are available on the potential interactions of efavirenz with the combination of saquinavir and ritonavir.

NRTIs:

Clinically significant interactions would not be expected since the NRTIs are metabolised via a different route than efavirenz and would be unlikely to compete for the same metabolic enzymes and elimination pathways.

NNRTIs:

No studies have been performed with efavirenz in combination with other NNRTIs and the potential for pharmacokinetic or pharmacodynamic interactions is unknown.

Antimicrobial agents:

Rifamycins: Rifampicin reduced efavirenz AUC by 26 % and C_{max} by 20 % in uninfected volunteers. The dose of efavirenz must be increased to 800 mg/day when taken with

rifampicin. No dose adjustment of rifampicin is recommended when given with efavirenz. In one study in uninfected volunteers, efavirenz induced a reduction in rifabutin C_{max} and AUC by 32 % and 38 % respectively. Rifabutin had no significant effect on the pharmacokinetics of efavirenz. These data suggest that the daily dose of rifabutin should be increased by 50 % when administered with efavirenz and that the rifabutin dose may be doubled for regimens in which rifabutin is given two or three times a week in combination with efavirenz.

Macrolide antibiotics:

Azithromycin:

No dosage adjustment is necessary when azithromycin is given in combination with efavirenz.

Clarithromycin:

No dose adjustment of efavirenz is recommended when given with clarithromycin.

Other macrolide antibiotics, such as erythromycin, have not been studied in combination with efavirenz.

Antifungal agents:

Voriconazole:

Co-administration of efavirenz and voriconazole is contraindicated.

Itraconazole:

Co-administration of efavirenz (600 mg orally once daily) with itraconazole (200 mg orally every 12 hours) in uninfected volunteers decreased the steady state AUC, C_{max},

and C_{min} of itraconazole by 39 %, 37 %, and 44 %, respectively, and of hydroxyitraconazole by 37 %, 35 %, and 43 %, respectively, compared to itraconazole administered alone. The pharmacokinetics of efavirenz were not affected. Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered.

Other antifungal agents:

No clinically significant pharmacokinetic interactions were seen when fluconazole and efavirenz were co‑administered to uninfected volunteers. The potential for interactions with efavirenz and other imidazole and triazole antifungals, such as itraconazole and ketoconazole, has not been studied.

Anticonvulsants:

Carbamazepine:

Co-administration of efavirenz (600 mg orally once daily) with carbamazepine (400 mg once daily) in uninfected volunteers resulted in a two-way interaction. The steady-state AUC, C_{max} and C_{min} of carbamazepine decreased by 27 %, 20 % and 35 %, respectively, while the steady-state AUC, C_{max} and C_{min} of efavirenz decreased by 36 %, 21 %, and 47 %, respectively. The steady-state AUC, C_{max} and C_{min} of the active carbamazepine epoxide metabolite remained unchanged. Carbamazepine plasma levels should be monitored periodically. There are no data with co-administration of higher doses of either medicinal product; therefore, no dose recommendation can be made, and alternative anticonvulsant treatment should be considered.

Other anticonvulsants:

No data are available on the potential interactions of efavirenz with phenytoin, phenobarbital, or other anticonvulsants that are substrates of CYP450 isozymes. When efavirenz is administered concomitantly with these agents, there is a potential for reduction or increase in the plasma concentrations of each agent; therefore, periodic monitoring of plasma levels should be conducted. Specific interaction studies have not been performed with efavirenz and vigabatrin or gabapentin. Clinically significant interactions would not be expected since vigabatrin and gabapentin are exclusively eliminated unchanged in the urine and would be unlikely to compete for the same metabolic enzymes and elimination pathways as efavirenz.

Lipid-lowering agents:

Co-administration of efavirenz with the HMG-CoA reductase inhibitors atorvastatin, pravastatin, or simvastatin has been shown to reduce the plasma concentration of the statin in uninfected volunteers. Cholesterol levels should be periodically monitored. Dosage adjustments of statins may be required.

Other interactions:

Antacids/famotidine:

Neither aluminium/magnesium hydroxide antacids nor famotidine altered the absorption of efavirenz in uninfected volunteers. These data suggest that alteration of gastric pH by other medicinal products would not be expected to affect efavirenz absorption.

Oral contraceptives:

Only the ethinyloestradiol component of oral contraceptives has been studied. The AUC following a single dose of ethinyloestradiol was increased (37 %) after multiple dosing of efavirenz. No significant changes were observed in C_{max} of ethinyloestradiol. The clinical

significance of these effects is not known. No effect of a single dose of ethinyloestradiol on efavirenz C_{max} or AUC was observed. Because the potential interaction of efavirenz with oral contraceptives has not been fully characterised, a reliable method of barrier contraception must be used in addition to oral contraceptives.

Methadone:

In a study of HIV infected IV 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. Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.

St. John's wort (*Hypericum perforatum*):

Plasma levels of efavirenz can be reduced by concomitant use of the herbal preparation St. John's wort (*Hypericum perforatum*). This is due to induction of drug metabolising enzymes and/or transport proteins by St. John's wort. Herbal preparations containing St. John's wort must not be used concomitantly with efavirenz. 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 and the dose of efavirenz may need adjusting. The inducing effect of St. John's wort may persist for at least 2 weeks after cessation of treatment.

Antidepressants:

There were no clinically significant effects on pharmacokinetic parameters when paroxetine and efavirenz were co-administered. No dose adjustments are necessary for either efavirenz or paroxetine when these medicinal products are co-administered. 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. Sertraline, a CYP3A4 substrate, did not significantly alter the pharmacokinetics of efavirenz. Efavirenz decreased sertraline C_{max}, C_{24} and AUC by 28,6 to 46,3 %. Sertraline dose increases should be guided by clinical response.

Cetirizine:

No dose adjustments are necessary for either efavirenz or cetirizine when these medicinal products are co-administered.

Lorazepam:

Efavirenz increased lorazepam C_{max} and AUC by 16,3 % and 7,3 % respectively. These changes are not considered to be clinically significant. No dose adjustments are necessary.

Calcium channel blockers:

No dosage adjustment is necessary for efavirenz when administered with diltiazem.

No data are available on the potential interactions of efavirenz with other calcium channel blockers that are substrates of the CYP3A4 enzyme (eg, verapamil, felodipine, nifedipine, nicardipine). When efavirenz is administered concomitantly with one of these agents, there is a potential for reduction in the plasma concentrations of the calcium channel blocker. Dose adjustments should be guided by clinical response (refer to the Summary of Product Characteristics for the calcium channel blocker).

PREGNANCY AND LACTATION:

Pregnancy:

Tenofovir disoproxil fumarate

No clinical data on exposed pregnancies are available for tenofovir disoproxil fumarate. Animal studies do not indicate direct or indirect harmful effects of tenofovir disoproxil fumarate with respect to pregnancy, fetal development, parturition or postnatal development.

Tenofovir disoproxil fumarate should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

However, given that the potential risks to developing human foetuses are unknown, the use of tenofovir disoproxil fumarate in women of childbearing potential must be accompanied by the use of effective contraception.

Lamivudine

The safety of lamivudine in human pregnancy has not been established. Reproductive studies in animals have not shown evidence of teratogenicity, and showed no effect on male or female fertility. Lamivudine induces early embryonic death when administered to pregnant rabbits at exposure levels comparable to those achieved in man. In humans, consistent with passive transmission of lamivudine across the placenta, lamivudine concentrations in infant serum at birth were similar to those in maternal and cord serum at delivery.

Although animal reproductive studies are not always predictive of the human response, administration is not recommended during the first three months of pregnancy.

Efavirenz

Pregnancy should be avoided in women treated with efavirenz. Barrier contraception should always be used in combination with other methods of contraception (for example, oral or other hormonal contraceptives). Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz. Efavirenz should not be used during pregnancy unless there are no other appropriate treatment options.

There are no adequate and well-controlled studies of efavirenz in pregnant women. In postmarketing experience through an antiretroviral pregnancy registry, more than 200 pregnancies with first-trimester exposure to efavirenz as part of a combination antiretroviral regimen have been reported with no specific malformation pattern. Retrospectively in this registry, a small number of cases of neural tube defects, including meningomyelocele, have been reported but causality has not been established. Studies in animals have shown reproductive toxicity including marked teratogenic effects.

Lactation:

Tenofovir disoproxil fumarate

In animal studies it has been shown that tenofovir is excreted into milk. It is not known whether tenofovir is excreted in human milk. Therefore, it is recommended that mothers being treated with tenofovir disoproxil fumarate do not breast-feed their infants. As a general rule, it is recommended that HIV infected women do not breast-feed their infants in order to avoid transmission of HIV to the infant.

Lamivudine

Following oral administration lamivudine was excreted in breast milk at similar concentrations to those found in serum. Since lamivudine and the virus pass into breast milk, it is recommended that mothers taking Lamivudine Tablets do not breast-feed their

infants. It is recommended that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

Efavirenz

Studies in rats have demonstrated that efavirenz is excreted in milk reaching concentrations much higher than those in maternal plasma. It is not known whether efavirenz is excreted in human milk. Since animal data suggest that the substance may be passed into breast milk, it is recommended that mothers taking efavirenz do not breast feed their infants. It is recommended that HIV infected women do not breast feed their infants under any circumstances in order to avoid transmission of HIV.

DOSAGE AND DIRECTIONS FOR USE:

Method of administration

Therapy should be initiated by a physician experienced in the management of HIV infection.

In exceptional circumstances in patients having particular difficulty in swallowing, **EFLATEN** can be administered following disintegration of the tablet in at least 100 ml of water, orange juice or grape juice.

Adults:

The recommended dose is one **EFLATEN** tablet once daily taken orally on an empty stomach.

It is recommended that Efavirenz be taken on an empty stomach. The increased efavirenz concentrations observed following administration of Efavirenz with food may lead to an increase in frequency of adverse events. In order to improve the tolerability of nervous system undesirable effects, bedtime dosing is recommended.

Children and adolescents:

The safety and efficacy of Tenofovir disoproxil fumarate in patients under the age of 18 years have not been established. Tenofovir disoproxil fumarate must not be administered to children or adolescents until further data become available describing the safety and efficacy of tenofovir disoproxil fumarate in patients under the age of 18 years. So, **EFLATEN** tablets are not recommended in children and adolescents.

Elderly:

No data are available on which to make a dose recommendation for patients over the age of 65 years.

Less than three months of age:

The limited data available are insufficient to propose specific dosage recommendations.

Renal insufficiency*:*

Tenofovir disoproxil fumarate

Tenofovir is eliminated by renal excretion and the exposure to tenofovir increases in patients with renal dysfunction. Dosing interval adjustment is required in all patients with creatinine clearance < 50 ml/min, as detailed below.

The proposed dose interval modifications are based on limited data and may not be optimal. The safety and efficacy of these dosing interval adjustment guidelines have not been clinically evaluated. Therefore, clinical response to treatment and renal function should be closely monitored in these patients.

	Creatinine Clearance (ml/min)*			**Haemodialysis Patients**
	50-80	**30-49**	**10-29**	
Recommended Tenofovir Disoproxil 245 mg Dosing Interval	Every 24 hours (no adjustment required)	Every 48 hours	Every 72 to 96 hours	Every 7 days following completion of a haemodialysis session**

* Calculated using ideal (lean) body weight

**Generally, once weekly dosing assuming three haemodialysis sessions per week, each of approximately 4 hours duration or after 12 hours cumulative haemodialysis.

No dosing recommendations could be drawn for non-haemodialysis patients with creatinine clearance< 10 ml/min.

Lamivudine

Lamivudine concentrations are increased in patients with moderate - severe renal impairment due to decreased clearance. The dose should therefore be adjusted, using oral solution presentation of Lamivudine Tablets for patients whose creatinine clearance falls below 30 ml/min.

Efavirenz

The pharmacokinetics of efavirenz have not been studies in patients with renal insufficiency; however, less than 1 % of an efavirenz dose is excreted unchanged in the urine, so the impact of renal impairment on efavirenz elimination should be minimal.

Hepatic impairment:

Tenofovir disoproxil fumarate

No dose adjustment is required in patients with hepatic impairment for tenofovir.

Lamivudine

Data obtained in patients with moderate to severe hepatic impairment shows that lamivudine pharmacokinetics are not significantly affected by hepatic dysfunction. Based on these data, no dose adjustment is necessary in patients with moderate or severe hepatic impairment unless accompanied by renal impairment.

Efavirenz

Patients with mild to moderate liver disease may be treated with their normally recommended dose of efavirenz. Patients should be monitored carefully for dose-related adverse events, especially nervous system symptoms.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Tenofovir disoproxil fumarate

Assessment of adverse reactions is based on post-marketing experience and experience in two studies in 653 treatment-experienced patients receiving treatment with tenofovir disoproxil fumarate (n = 443) or placebo (n = 210) in combination with other

antiretroviral medicinal products for 24 weeks and also in a double-blind comparative controlled study in which 600 treatment-naïve patients received treatment with tenofovir disoproxil 245 mg (as fumarate) (n = 299) or stavudine (n = 301) in combination with lamivudine and efavirenz for 144 weeks.

Approximately one third of patients can be expected to experience adverse reactions following treatment with tenofovir disoproxil fumarate in combination with other antiretroviral agents. These reactions are usually mild to moderate gastrointestinal events.

The adverse reactions with suspected (at least possible) relationship to 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) or very rare (< 1/10,000) including isolated reports, or not known (identified through post-marketing safety surveillance and the frequency cannot be estimated from the available data).

Metabolism and nutrition disorders:

Very common: hypophosphataemia

Rare: lactic acidosis

Nervous system disorders:

Very common: dizziness

Respiratory, thoracic and mediastinal disorders:

Very rare: dyspnoea

Gastrointestinal disorders:

Very common: diarrhoea, nausea, vomiting

Common: flatulence

Rare: pancreatitis

Hepatobiliary disorders:

Rare: increased transaminases

Very rare: hepatitis

Skin and subcutaneous tissue disorders:

Rare: rash

Musculoskeletal and connective tissue disorders:

Not known: myopathy, osteomalacia (both associated with proximal renal tubulopathy)

Renal and urinary disorders:

Rare: renal failure, acute renal failure, proximal tubulopathy (including Fanconi syndrome), increased creatinine

Very rare: acute tubular necrosis

Not known: nephritis (including acute interstitial nephritis), nephrogenic diabetes insipidus.

General disorders and administration site conditions:

Very rare: asthenia

Approximately 1 % of tenofovir disoproxil fumarate treated patients discontinued treatment due to the gastrointestinal events.

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia.

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).

In a 144-week controlled clinical study in antiretroviral-naïve patients that compared tenofovir disoproxil fumarate with stavudine in combination with lamivudine and efavirenz, patients who received tenofovir disoproxil had a significantly lower incidence of lipodystrophy compared with patients who received stavudine. The tenofovir disoproxil fumarate arm also had significantly smaller mean increases in fasting triglycerides and total cholesterol than the comparator arm.

In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise.

Lamivudine:

The following adverse reactions have been reported during therapy for HIV disease with Lamivudine.

The adverse reactions 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 (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Blood and lymphatic systems disorders

Uncommon: Neutropenia and anaemia (both occasionally severe), thrombocytopenia

Very rare: Pure red cell aplasia

Nervous system disorders

Common: Headache, insomnia

Very rare: Peripheral neuropathy (or paraesthesia)

Respiratory, thoracic and mediastinal disorders

Common: Cough, nasal symptoms

Gastrointestinal disorders

Common: Nausea, vomiting, abdominal pain or cramps, diarrhoea

Rare: Pancreatitis. Elevations in serum amylase.

Hepatobiliary disorders

Uncommon: Transient elevations in liver enzymes (AST, ALT).

Rare: Hepatitis

Skin and subcutaneous tissue disorders

Common: Rash, alopecia

Musculoskeletal and connective tissue disorders

Common: Arthralgia, muscle disorders

Rare: Rhabdomyolysis

General disorders and administration site conditions

Common: Fatigue, malaise, fever.

Cases of lactic acidosis, sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of nucleoside analogues.

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia.

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise.

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term combined antiretroviral exposure (CART). The frequency of which is unknown.

Efavirenz

Adverse reactions of moderate or greater severity with at least possible relationship to treatment regimen (based on investigator attribution) reported in clinical trials of efavirenz at the recommended dose in combination therapy (n = 1,008) are listed below. Frequency is defined using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000) including isolated reports.

Immune system disorders

Uncommon: Hypersensitivity

Psychiatric disorders

Common: Anxiety, depression

Uncommon: Affect lability, aggression, euphoric mood, hallucination, mania, paranoia, suicide attempt, suicide ideation

Nervous system disorders

Common: Abnormal dreams, disturbance in attention, dizziness, headache, insomnia, somnolence

Uncommon: Agitation, amnesia, ataxia, coordination abnormal, confusional state, convulsions, thinking abnormal

Eye disorders

Uncommon: Vision blurred

Ear and labyrinth disorders

Uncommon: Vertigo

Gastrointestinal disorders

Common: Abdominal pain, diarrhoea, nausea, vomiting

Uncommon: Pancreatitis acute

Hepatobiliary disorders

Uncommon: Hepatitis acute

Skin and subcutaneous tissue disorders

Very common: Rash

Common: Pruritus

Uncommon: Erythema multiforme

General disorders and administration site conditions

Common: Fatigue

Reproductive system and breast disorders

Uncommon: Gynaecomastia

Immune Reactivation Syndrome:

In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise.

Lipodystrophy and metabolic abnormalities:

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia.

Osteonecrosis:

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

Laboratory test abnormalities:

Liver enzymes:

Elevations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) to greater than five times the upper limit of the normal range (ULN) were seen in 3 % of 1,008 patients treated with 600 mg of efavirenz (5‑8 % after long-term treatment in study 006). Similar elevations were seen in patients treated with control regimens (5 % after long-term treatment). Elevations of gamma‑glutamyltransferase (GGT) to greater than five times ULN were observed in 4 % of all patients treated with 600 mg of

efavirenz and 1,5–2 % of patients treated with control regimens (7 % of efavirenz-treated patients and 3 % of control-treated patients after long-term treatment). Isolated elevations of GGT in patients receiving efavirenz may reflect enzyme induction. In the long-term study (006), 1 % of patients in each treatment arm discontinued because of liver or biliary system disorders.

In the long-term data set from study 006, 137 patients treated with efavirenz-containing regimens (median duration of therapy, 68 weeks) and 84 treated with a control regimen (median duration, 56 weeks) were seropositive at screening for hepatitis B (surface antigen positive) and/or C (hepatitis C antibody positive). Among these co-infected patients, elevations in AST to greater than five times ULN developed in 13 % of patients in the efavirenz arms and 7 % of those in the control arm, and elevations in ALT to greater than five times ULN developed in 20 % of patients in the efavirenz arms and 7 % of the patients in the control arm. Among co-infected patients, 3 % of those treated with efavirenz-containing regimens and 2 % in the control arm discontinued from the study because of liver or biliary system disorders. Reasons for discontinuation among co-infected recipients of efavirenz included abnormalities in hepatic enzymes; there were no discontinuations reported in this study for cholestatic hepatitis, hepatic failure, or fatty liver.

Amylase:

In the clinical trial subset of 1,008 patients, asymptomatic increases in serum amylase levels greater than 1,5 times the upper limit of normal were seen in 10 % of patients treated with efavirenz and 6 % of patients treated with control regimens. The clinical significance of asymptomatic increases in serum amylase is unknown.

Lipids:

Increases in total cholesterol of 10-20 % have been observed in some uninfected volunteers receiving efavirenz. In clinical trials of various efavirenz-containing regimens in treatment naive patients, total cholesterol, HDL-cholesterol, and triglycerides increased over 48 weeks of treatment (21-31 %, 23-34 %, and 23-49 %, respectively). The proportion of patients with a total cholesterol/HDL-cholesterol ratio greater than 5 was unchanged. The magnitude of changes in lipid levels may be influenced by factors such as duration of therapy and other components of the antiretroviral regimen.

Cannabinoid test interaction:

Efavirenz does not bind to cannabinoid receptors. False positive urine cannabinoid test results have been reported in uninfected volunteers who received efavirenz. False positive test results have only been observed with the CEDIA DAU Multi‑Level THC assay, which is used for screening, and have not been observed with other cannabinoid assays tested including tests used for confirmation of positive results.

Post marketing experience with efavirenz has shown the following additional adverse events to occur in association with efavirenz-containing antiretroviral treatment regimens: delusion, gynaecomastia, hepatic failure, neurosis, photoallergic dermatitis, psychosis and completed suicide.

Special Precautions:

Effects on ability to drive and use machines:

No studies on the effects on the ability to drive or use machines have been performed. However, patients should be informed that dizziness has been reported during treatment with tenofovir disoproxil fumarate. Efavirenz may cause dizziness, impaired

concentration, and/or somnolence. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery.

Lactose:

The fixed-dose combination (Tenofovir/Lamivudine/Efavirenz) Tablets are unsuitable for individuals with the rare hereditary disorders of galactosaemia or glucose/galactose malabsorption syndrome.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Tenofovir disoproxil fumarate:

If overdose occurs the patient must be monitored for evidence of toxicity and standard supportive treatment applied as necessary.

Tenofovir can be removed by haemodialysis; the median haemodialysis clearance of tenofovir is 134 ml/min. The elimination of tenofovir by peritoneal dialysis has not been studied.

Lamivudine:

Administration of lamivudine at very high dose levels in acute animal studies did not result in any organ toxicity. Limited data are available on the consequences of ingestion of acute overdoses in humans. No fatalities occurred, and the patients recovered. No specific signs or symptoms have been identified following such overdose.

If overdosage occurs the patient should be monitored, and standard supportive treatment applied as required. Since lamivudine is dialysable, continuous haemodialysis could be used in the treatment of overdosage, although this has not been studied.

Efavirenz

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

Treatment of overdose with efavirenz should consist of general supportive measures, including monitoring of vital signs and observation of the patient's clinical status. 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.

IDENTIFICATION:

White, capsule shaped, film-coated tablets, debossed with “M152” on one side and plain on the other side.

PRESENTATION:

EFLATEN is packed in high density propylene (HDPE) bottle pack comprising of white opaque wide mouth HDPE bottle with a white opaque polypropylene (PP) screw closure with desiccant packed in an outer carton in 28’s, 30’s and 100’s pack.*

*Not all packs may be marketed

EFLATEN is packed in high density propylene (HDPE) bottle pack comprising of blue opaque wide mouth HDPE bottle with a blue opaque polypropylene (PP) screw closure with desiccant packed in an outer carton in 28’s and 30’s pack.

STORAGE INSTRUCTIONS:

Store at or below 30 ^{o}C. Store in the original container. Do not remove from the carton until required for use. Keep the bottles tightly closed.

KEEP OUT OF REACH AND SIGHT OF CHILDREN.

REGISTRATION NUMBER:

45/20.2.8/0171

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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DATE OF PUBLICATION OF THE PACKAGE INSERT:

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