SUMMARY OF PRODUCT CHARACTERISTIC

1. Name of the Medicinal Product

Lamivudine 300mg and Tenofovir Disoproxil Fumarate 300 mg Tablets

2. Qualitative and Quantitative Composition

Each film-coated tablet contains:
Lamivudine USP ……300 mg
Tenofovir Disoproxil Fumarate ..300 mg
For Excipients see point 6.1

3. Pharmaceutical Form

Film coated Tablet

4. Clinical Particulars

4.1 Therapeutic indications

Lamivudine and Tenofovir Disoproxil Fumarate tablet is indicated, in combination with atleast one other antiretroviral agents, for the treatment of HIV-1 infection in adults over 18 yrs of age.

4.2 Posology and method of administration

Adults:

The dose of Lamivudine and Tenofovir tablet is one tablet once daily taken orally. In order to optimise the absorption of tenofovir, it is recommended that Lamivudine/ Tenofovir Disoproxil Fumarate 300mg /300mg Tablets be taken with food.

Paediatric Patients:

Lamivudine/Tenofovir Disoproxil Fumarate 300mg/300mg Tablets is not recommended for use in children and adolescents below the age of 18 years due to insufficient data on safety and efficacy.

Elderly:

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

Renal impairment:

Lamivudine/Tenofovir Disoproxil Fumarate 300mg/300mg Tablets is not recommended for use in patients with a creatinine clearance < 50 ml/min, as appropriate dose adjustments are not possible. For these patients, separate formulations of lamivudine and tenofovir disoproxil fumarate should be used.

Discontinuation of therapy:

If Lamivudine/Tenofovir Disoproxil Fumarate 300mg/300mg Tablets is discontinued in patients with chronic hepatitis B (with or without HIV co-infection), the patient should be closely monitored for evidence of exacerbation of hepatitis.

4.3 Contraindications

Contraindicated in patients with previously demonstrated hypersensitivity to any active substances or to any of the excipients of the product.

4.4 Special warnings and precautions for use

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

HBV antibody testing should be offered to all HIV infected patients before initiating tenofovir therapy. Patients must be advised that tenofovir has not been proven to prevent the transmission of HIV or HBV to others through sexual contact or contamination with blood. Appropriate precautions must continue to be used.

Co-administration of other medicinal products: Lamivudine/ Tenofovir Disoproxil Fumarate 300mg /300mg Tablets should not be administered with any other medicinal products containing tenofovir disoproxil fumarate, adefovir dipivoxil, lamivudine or emtricitabine.

Co-administration of tenofovir disoproxil fumarate and didanosine is not recommended, as this may increase the risk of didanosine-related adverse events.

Rare cases of pancreatitis and lactic acidosis, sometimes fatal, have been reported. Furthermore, co-administration of tenofovir disoproxil fumarate and didanosine at a dose of 400 mg daily has been associated with a significant decrease in CD4 cell count, possibly due to an intracellular interaction increasing phosphorylated (i.e. active) didanosine. A decreased dosage of 250 mg didanosine co-administered with tenofovir disoproxil fumarate therapy has been associated with reports of high rates of virological failure within several tested combinations for the treatment of HIV-1 infection.

Triple therapy with nucleosides/nucleotides: There have been reports of a high rate of virological failure and of emergence of resistance at early stage in HIV patients when tenofovir disoproxil fumarate and lamivudine was combined with abacavir or didanosine.

***Renal function*:** Tenofovir is primarily excreted by the kidneys through a combination of glomerular filtration and active tubular secretion. Thus, clearance is decreased in patients with impaired renal function. There are limited data on the safety and efficacy of tenofovir disoproxil fumarate in patients with impaired renal function (<80 ml/min). In such patients, Lamivudine/ Tenofovir Disoproxil Fumarate 300mg /300mg Tablets should only be used if the potential benefits of treatment are considered to outweigh the potential risks.

In patients with moderate to severe renal impairment, the plasma half-life of lamivudine is increased due to decreased clearance. Decreased doses are recommended for patients with creatinine clearance <50 ml/min.

The use of Lamivudine/Tenofovir Disoproxil Fumarate 300mg/300mg Tablets is not recommended in patients with creatinine clearance < 50 ml/min, since appropriate dose reductions cannot be achieved with the combination tablet.

Renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir disoproxil fumarate in clinical practice. It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with Lamivudine/ Tenofovir Disoproxil

Fumarate 300mg /300mg Tablets. Routine monitoring of calculated creatinine clearance and serum phosphate should be performed in patients at risk for renal impairment.

In patients receiving tenofovir disoproxil fumarate renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations, if serum phosphate is <1.5 mg/dl (0.48 mmol/l) or creatinine clearance decreases below 50 ml/min. Consideration should also be given to interrupting treatment with Lamivudine/ Tenofovir Disoproxil Fumarate 300mg /300mg Tablets in patients whose creatinine clearance falls below 50 ml/min or whose serum phosphate decreases below 1.0 mg/dl (0.32 mmol/l)

Lamivudine/ Tenofovir Disoproxil Fumarate 300mg /300mg Tablets should be avoided with concurrent use of a nephrotoxic medicinal product (e.g. aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2). If concomitant use of tenofovir disoproxil fumarate and nephrotoxic agents is unavoidable, renal function should be monitored weekly.

Bone effects: In a controlled clinical study decreases in bone mineral density of spine and changes in bone biomarkers from baseline were observed in both treatment groups, but were significantly greater in the tenofovir disoproxil fumarate treatment group than in the comparator group treated with stavudine (each in combination with lamivudine and efavirenz) at 144 weeks. Decreases in bone mineral density of hip were significantly greater in this group until 96 weeks. However, there was no increased risk of fractures or evidence for clinically relevant bone abnormalities over 144 weeks.

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

Osteonecrosis: although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body

mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Patients with HIV and hepatitis B or C virus co-infection: Patients with chronic hepatitis B or C treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. Physicians should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV).

Lamivudine and tenofovir have anti-HBV activity when used in antiretroviral combination therapy to control HIV infection. The combination of tenofovir disoproxil fumarate 300 mg and lamivudine 300 mg has not been studied for the treatment of HBV. Lamivudine/Tenofovir Disoproxil Fumarate 300mg/300mg Tablets is not indicated for the treatment of chronic HBV infection.

Discontinuation of therapy with Lamivudine/Tenofovir Disoproxil Fumarate 300mg/300mg Tablets 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 Lamivudine/ Tenofovir Disoproxil Fumarate 300mg /300mg Tablets should be closely monitored with both clinical and laboratory follow-up for at least six months after stopping treatment. 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 disease*:** 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 is a rare but severe, potentially life-threatening complication associated with use of nucleoside reverse transcriptase inhibitors (NRTI). Several other agents of this class are known to cause lactic acidosis. Preclinical and clinical data suggest that the risk of occurrence of lactic acidosis, a class effect of nucleoside analogues, is very low for tenofovir disoproxil fumarate. However, this risk cannot be excluded, as tenofovir is structurally related to nucleoside analogues. Lactic acidosis may occur after a few to several months of NRTI treatment. Patients with hyperlactataemia may be asymptomatic, critically ill, or may have non-specific symptoms such as dyspnoea, fatigue, nausea, vomiting, diarrhoea and abdominal pain. Risk factors for NRTI-related lactic acidosis include female gender and obesity. Patients at increased risk should be closely monitored clinically. Screening for hyperlactataemia in asymptomatic patients treated with NRTIs, however, is not recommended. Symptomatic patients usually have levels > 5 mmol/l and require discontinuation of all NRTIs. Lactic acid levels > 10 mmol/l usually are a medical emergency.

Lipodystrophy**:** Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV-infected patients. Whereas for some other antiretrovirals there is considerable evidence for this adverse reaction, the evidence for tenofovir as a causative agent is weak; indeed switching from a thymidine analogue (e.g. stavudine) to tenofovir has been shown to increase limb fat in patients with lipoatrophy. A higher risk of lipodystrophy has been associated e.g. with older age of the patient, longer duration of antiretroviral therapy and related metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Measurement of fasting serum lipids and blood glucose as well as appropriate management of lipid disorders should be considered.

Mitochondrial dysfunction**:** Nucleoside and nucleotide analogues have been demonstrated, *in vitro* and *in vivo,* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed *in utero* and/or postnatally to nucleoside analogues. The main adverse events reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactataemia, hyperlipasaemia). These events are often

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

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

Immune Reactivation Syndrome: in HIV-infected patients with pre-existing severe immune deficiency, typically in the first few weeks or months after initiation of combination ART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens (e.g. CMV retinitis, mycobacterial infections, Pneumocystis pneumonia) may arise and cause serious clinical conditions or aggravation of symptoms. Treatment should be instituted when necessary.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

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

Interactions relevant to lamivudine: Co-administration with trimethoprim/ sulfamethoxazole results in a 40% increase in lamivudine area under the concentration curve. No dose adjustment of Lamivudine/Tenofovir Disoproxil Fumarate 300mg /300mg Tablets is necessary. Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole.

Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another. Therefore, use of lamivudine in combination with zalcitabine is not recommended.

***Interactions relevant to tenofovir*:**

Didanosine: Co-administration of tenofovir disoproxil fumarate and didanosine is not recommended.

Renally eliminated medicinal products: Since tenofovir is primarily eliminated by the kidneys, co-administration of tenofovir disoproxil fumarate with medicinal products that reduce renal function or compete for active tubular secretion via transport proteins hOAT 1, hOAT 3 or MRP 4 (e.g. cidofovir) may increase serum concentrations of tenofovir and/or the co-administered medicinal products.

Tenofovir disoproxil fumarate should be avoided with concurrent use of a nephrotoxic medicinal product. Some examples include, but are not limited to, aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2.

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

Other interactions:

Interactions between Lamivudine/Tenofovir Disoproxil Fumarate 300mg/300mg Tablets and HIV protease inhibitors, as well as antiviral agents other than protease inhibitors, are listed in Table below (increased exposure is indicated as "↑", decreased exposure as "↓", no change as "↔", twice daily as "b.i.d.", and once daily as "q.d.").

Table: Interactions between tenofovir disoproxil fumarate and other medicinal products

Medicinal products by therapeutic areas (dose in mg)	Effects on drug levels Mean % change in UC, C_{max}, C_{min}	Recommendation concerning co-administration with tenofovir disoproxil fumarate 300 mg
ANTI-INFECTIVES		
Antiretrovirals		
Protease inhibitors:		
Atazanavir (400 mg q.d.)	Atazanavir: AUC: ↓ 25% Cmax: ↓ 21% Cmin: ↓ 40% Tenofovir: AUC: ↑ 24% Cmax: ↑ 14% Cmin: ↑ 22%	If atazanavir and Lamivudine/Tenofovir Disoproxil Fumarate 300mg/300mg Tablets are coadministered, atazanavir should be given at the dose 300 mg q.d. together with ritonavir 100 mg q.d.
Atazanavir/ Ritonavir (300 mg/100 mg q.d.)	Atazanavir: AUC: ↓ 25% Cmax: ↓ 28% Cmin: ↓ 26% Tenofovir: AUC: ↑ 37% Cmax: ↑ 34% Cmin: ↑ 29%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir associated adverse events, including renal disorders. Renal function should be closely monitored.
Lopinavir/ Ritonavir (400 mg/100 mg b.i.d.)	Lopinavir/ ritonavir: No significant effect on lopinavir/ ritonavir PK parameters. Tenofovir: AUC: ↑ 32% Cmax: ↔ Cmin: ↑ 51%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir associated adverse events, including renal disorders. Renal function should be closely monitored.
Darunavir/ Ritonavir (300 mg/100 mg b.i.d.)	Darunavir: No significant effect on darunavir/ ritonavir PK parameters. Tenofovir: AUC: ↑ 22% Cmin: ↑ 37%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir associated adverse events, including renal disorders. Renal function should be closely monitored.
NRTIs		
Didanosine (400 mg q.d.)	Didanosine AUC ↑ 40-60%	The risk of didanosine-related adverse effects (e.g., pancreatitis, lactic acidosis appears to be increased, and CD4 cells may decrease significantly on co-

		administration. Also didanosine at 250 mg co-administered with tenofovir within several different antiretroviral combination regimens has been associated with a high rate of virological failure. Co-administration of Lamivudine/Tenofovir Disoproxil Fumarate 300mg/300mg Tablets and didanosine is not recommended.
Adefovir dipivoxil	AUC: ↔ Cmax: ↔	Lamivudine/Tenofovir Disoproxil Fumarate 300mg/300mg Tablets should not be administered concurrently with adefovir dipivoxil.
Entecavir (1 mg q.d.)	AUC: ↔ Cmax: ↔	No clinically significant pharmacokinetic interactions when Lamivudine/Tenofovir Disoproxil Fumarate 300mg/300mg Tablets is co-administered with entecavir.

Studies conducted with other medicinal products: There were no clinically significant pharmacokinetic interactions when Lamivudine/Tenofovir Disoproxil Fumarate 300mg/300mg Tablets is co-administered with indinavir, efavirenz, nelfinavir, saquinavir (ritonavir boosted), methadone, ribavirin, rifampicin, tacrolimus, or the hormonal contraceptive norgestimate/ethinyl oestradiol.

Food effect: Tenofovir disoproxil fumarate must be taken with food, as food enhances the bioavailability of tenofovir.

4.6 Pregnancy and lactation

Pregnancy:

Animal studies do not indicate direct or indirect harmful effects of tenofovir disoproxil fumarate with respect to pregnancy, foetal development, parturition or postnatal development. In humans, the safety of tenofovir in pregnancy has not been fully established. Sufficient numbers of first trimester exposures have been monitored, however, to detect at least a twofold increase in the risk of overall birth defects. No increase in birth defects was seen.

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

Lamivudine/ Tenofovir Disoproxil Fumarate 300mg /300mg Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

***Nursing Mothers*:**

In animal studies it has been shown that tenofovir is excreted into milk. It is not known whether tenofovir is excreted in human milk. Lamivudine is excreted into the breast milk of lactating mothers.

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.

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, patients should be informed that dizziness has been reported during treatment with tenofovir disoproxil fumarate.

4.8 Undesirable effects

Lamivudine:

Adverse events considered at least possibly related to treatment with lamivudine 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), unknown (frequency cannot be estimated from the available data).

Blood and lymphatic systems disorders:

Uncommon: neutropenia, anaemia (occasionally severe), thrombocytopenia

Very rare: pure red cell aplasia

Metabolism and nutrition disorders:

Very common: hypophosphataemia

Rare: lactic acidosis

Unknown: hypokalaemia

Nervous system disorders:

Very common: dizziness

Common: headache and insomnia

Very rare: peripheral neuropathy (paraesthesia)

Respiratory, thoracic and mediastinal disorders:

Common: cough, nasal symptoms

Very rare: dyspnoea

Gastrointestinal disorders:

Very common: diarrhoea, nausea, vomiting

Common: abdominal pain/cramps, flatulence

Rare: pancreatitis, elevated serum amylases

Hepatobiliary disorders:

Uncommon: transient elevation in liver enzymes

Rare: hepatitis

Unknown: hepatic steatosis

Skin and subcutaneous tissue disorders:

Common: Rash, hair loss

Musculoskeletal and connective tissue disorders:

Common: arthralgia, muscle disorder

Unknown: rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), muscular weakness, myopathy, osteonecrosis

Renal and urinary disorders:

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

Very rare: acute tubular necrosis

Unknown: nephritis (including acute interstitial nephritis), nephrogenic diabetes insipidus

General disorders and administration site disorders:

Common: fatigue, malaise, fever

Very rare: asthenia

Unknown: immune reconstitution syndrome

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: 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 tenofovir disoproxil fumarate therapy in the absence of proximal renal tubulopathy.

Tenofovir:

Immune system disorders: Allergic reaction

Metabolism and nutrition disorders: Hypophosphate- mia, lactic acidosis, hypokalemia.

Respiratory, thoracic and mediastinal disorders: Dyspnea

Gastrointestinal disorders: Abdominal pain, pancreatitis, increased amylase.

Renal and urinary disorders: Renal insufficiency, Renal failure, Acute renal failure, Fanconi syndrome, Proximal tubulopathy, Proteinuria, Increased creatinine, Acute tubular necrosis, Nephrogenic diabetes insipidus, Polyuria, Interstitial nephritis (including acute cases).

Hepatobiliary Disorders: hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT gamma GT)

Skin and subcutaneous tissue disorders: Rash

Musculoskeletal and connective tissue disorders: rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy

General disorders and administration site conditions: Asthenia

In HBV infected patients, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of HBV therapy.

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hyper-triglyceridaemia, 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).

4.9 Overdose

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. Because a negligible amount of lamivudine was removed via (4-hour) haemodialysis,

continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous haemodialysis would provide clinical benefit in a lamivudine overdose event.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for treatment of HIV infections, combinations .

ATC Code: J05AR

Lamivudine: Lamivudine is a synthetic nucleoside analogue. Intracellularly, lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is inhibition of reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue. 3TC-TP is a weak inhibitor of mammalian DNA polymerases alpha and beta, and mitochondrial DNA polymerase- gamma.

Tenofovir: Tenofovir disoproxil fumarate is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir disoproxil fumarate requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases alpha and beta, and mitochondrial DNA polymerase gamma.

***Resistance*:** 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. Clinical studies in treatment-experienced patients have assessed the anti-HIV activity of tenofovir against strains of HIV-1 with thymidine analogue mutations (TAMs),

which are not selected for by tenofovir. Patients whose HIV expressed 3 or more TAMs that included either the M41L or L210W mutation showed reduced response to tenofovir.

In many cases when a lamivudine-containing treatment regimen fails (though less often when the treatment regimen contains a ritonavir-boosted protease inhibitor), 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. M184V causes high-level resistance to lamivudine (>300-fold reduced susceptibility). *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. Therefore, maintaining lamivudine therapy despite emergence of M184V mutation should only be considered when the activity of the best available NRTI backbone is significantly compromised.

Cross-resistance conferred by the M184V mutation is limited within the nucleoside/nucleotide inhibitor class of antiretroviral 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.

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

5.2 Pharmacokinetic properties

Lamivudine: Lamivudine is rapidly absorbed following oral administration. Bioavailability is between 80 and 85%. Following single dose administration of Lamivudine/ Tenofovir Disoproxil Fumarate 300mg/ 300mg Tablets in healthy volunteers, the mean (±SD) lamivudine C_{max} value was 2.24 µg/ml (±0.69) and the corresponding value for AUC was 10.54 µg.h/ml (±2.94). The mean (±SD) lamivudine T_{max} value was 2.15 hours (± 0.87).

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

Metabolism: Metabolism of lamivudine is a minor route of elimination. Lamivudine is predominantly cleared unchanged by renal excretion. The likelihood of metabolic drug interactions with lamivudine is low due to the small extent of hepatic metabolism (5 - 10%) and low plasma protein binding.

Elimination: The observed lamivudine half-life of elimination is 5 to 7 hours. The half-life of intracellular lamivudine triphosphate has been estimated to approximately 22 hours. The mean systemic clearance of lamivudine is approximately 0.32 l/h/kg, with predominantly renal clearance (> 70%), including tubular secretion through the organic cationic transport system.

Special populations:

Renal impairment: Studies in patients with renal impairment show that lamivudine elimination is affected by renal dysfunction. Dose reduction is recommended for patients with creatinine clearance ≤50 ml/min.

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. Following single dose administration of Lamivudine/Tenofovir Disoproxil Fumarate 300mg /300mg Tablets in healthy volunteers, the mean (±SD) tenofovir C_{max} value was 312 ng/ml (±68) and the corresponding value for AUC was 2754 ng.h/ml (±586). The mean (±SD) tenofovir T_{max} value was 2.06 (± 0.61) hours.

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%. However, administration of tenofovir disoproxil fumarate with a light meal did not have a significant effect on the pharmacokinetics of tenofovir.

Distribution: *In vitro* protein binding of tenofovir to plasma or serum protein was less than 0.7 and 7.2%, respectively, over the tenofovir concentration range 0.01 to 25 µg/ml.

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

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

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

Renal impairment: Pharmacokinetic parameters of tenofovir were determined following administration of a single dose of tenofovir disoproxil fumarate 300 mg to 40 non-HIV, non-HBV infected patients with varying degrees of renal impairment defined according to baseline creatinine clearance (CrCl) (normal renal function when CrCl > 80 ml/min; mild with CrCl = 50-79 ml/min; moderate with CrCl = 30-49 ml/min and severe with CrCl = 10-29 ml/min). Compared with patients with normal renal function, the mean (%CV) tenofovir exposure increased from 2,185 (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 fumarate 300 mg 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 300 mg dose of tenofovir disoproxil fumarate was administered to non-HIV, non-HBV infected patients with varying degrees of hepatic impairment defined according to Child-Pugh-Turcotte (CPT) classification. Tenofovir pharmacokinetic parameters were not substantially altered in subjects with hepatic impairment suggesting that no dose adjustment is required in these subjects. 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 2,31 (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: Tenofovir diphosphate has an intracellular half-life of 10 hours in activated and 50 hours in resting peripheral blood mononuclear cells (PBMCs).

5.3 Preclinical safety data

Lamivudine: Administration of lamivudine in animal toxicity studies at high doses was not associated with any major organ toxicity. Lamivudine was not mutagenic in bacterial tests, but showed activity in an *in vitro* cytogenetic assay and the mouse lymphoma assay. Lamivudine was not genotoxic *in vitro* at doses that gave plasma concentrations around 40-50 times higher than the anticipated clinical plasma levels. As the *in vitro* mutagenic activity of lamivudine could not

be confirmed in *in vivo* tests, it is concluded that lamivudine should not represent a genotoxic hazard to patients undergoing treatment. The results of long-term carcinogenicity studies in rats and mice did not show any carcinogenic potential relevant for humans. In a study of reproductive performance, lamivudine administered to rats at doses up to 4,000 mg/kg/day, producing plasma levels 47 to 70 times those in humans, revealed no evidence of impaired fertility and no effect on the survival, growth, and development to weaning of the offspring.

Tenofovir: Preclinical studies conducted in rats, dogs and monkeys revealed target organ effects in gastrointestinal tract, kidney, bone and a decrease in serum phosphate concentration. Bone toxicity was diagnosed as osteomalacia (monkeys) and reduced bone mineral density (rats and dogs). Findings in the rat and monkey studies indicated that there was a substance-related decrease in intestinal absorption of phosphate with potential secondary reduction in bone mineral density. However, no conclusion could be drawn on the mechanism(s) underlying these toxicities.

Reproductive studies were conducted in rats and rabbits. There were no effects on mating or fertility parameters or on any pregnancy or foetal parameter. There were no gross foetal alterations of soft or skeletal tissues. Tenofovir disoproxil fumarate reduced the viability index and weight of pups in peri-post natal toxicity studies.

Genotoxicity studies have shown that tenofovir disoproxil fumarate was negative in the *in vivo* mouse bone marrow micronucleus assay but was positive for inducing forward mutations in the *in vitro* L5178Y mouse lymphoma cell assay in the presence or absence of S9 metabolic activation. Tenofovir disoproxil fumarate was positive in the Ames test (strain TA 1535) in two out of three studies, once in the presence of S9 mix (6.2- to 6.8-fold increase) and once without S9 mix. Tenofovir disoproxil fumarate was also weakly positive in an *in vivo* / *in vitro* unscheduled DNA synthesis test in primary rat hepatocytes.

Tenofovir disoproxil fumarate did not show any carcinogenic potential in a long-term oral carcinogenicity study in rats. A long-term oral carcinogenicity study in mice showed a low incidence of duodenal tumours, considered likely related to high local concentrations of tenofovir disoproxil fumarate in the gastrointestinal tract at a dose of 600 mg/kg/day. While the mechanism of tumour formation is uncertain, the findings are unlikely to be of relevance to humans.

6. Pharmaceutical Particulars

6.1 List of Excipients

The other ingredients are: Microcrystalline cellulose, Croscarmellose sodium, Magnesium Stearate. Colour contains, Lactose monohydrate, Hypromellose, Titanium Dioxide, Triacetin

6.2 Incompatibilities

Not applicable for Oral Solid dosage form.

6.3 Shelf life

24 Months.

6.4 Special precautions for storage

Store at a temperature not exceeding 30 °C in the original package, protected from Light.

As with all medicines, keep this product out of the reach of children.

6.5 Nature and contents of container

Following minimum batch details is coded on Container Label and Carton
Batch No., Mfg. Date and Exp. Date.

6.6 Special Precaution for disposal

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

7. Supplier

Macleods Pharmaceuticals Ltd.
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8. WHO Reference Number (Prequalification Programme)

9. Date of first Prequalification/ last renewal

10. Date of Revision of the Text:

References:

SUMMARY OF PRODUCT CHARACTERISTIC

1. SMPC: Lamivudine/Tenofovir disoproxil fumarate tablets, 300/300mg (Matrix Lab Ltd.), HA414, WHOPAR part 4 11/2010, version 1.0; available at site: http://apps.who.int/prequal/WHOPAR/WHOPARPRODUCTS/HA414Part4v1.pdf, accessed on 18/04/2011.
2. Tenvir-L Pack Insert, November 2009, available at http://www.cipladoc.com/ therapeutic /pdf_cipla/tenvir_l.pdf, accessed on 18/04/2011.