SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF MEDICINAL PRODUCT

Tenofovir Disoproxil Fumarate Tablets 300mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains
Tenofovir Disoproxil fumarate……300mg
equivalent to Tenofovir Disoproxil…….245mg

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film coated tablets.

Light blue capsule shaped biconvex, film coated tablets debossed with ‘’TNV” on one side and plain on the other side
The tablets should not be divided

4. CLINICAL PATIRCULARS

4.1 Therapeutic indications

HIV-1 infection: Texavir is indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected adults over 18 years of age.

The choice of Texavir to treat antiretroviral experienced patients with HIV-1 infection should be based on individual viral resistance testing and/or the treatment of history of the patient.

Consideration should be given to official treatment guidelines for HIV-1 infection (e.g by WHO).

Hepatitis B infection: Texavir is indicated to the treatment of chronic hepatitis B in adults with compensated liver disease, with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis.

Consideration should be given to official treatment guidelines for HBV infection

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the management of HIV infection and/or treatment of chronic Hepatitis B.

Adults: The recommended dose for treatment of HIV and for the treatment of chronic Hepatitis B is 300mg tenofovir disoproxil fumarate (one tablet) once daily taken orally with food.
Chronic Hepatitis B: The optimal duration of treatment is unknown. Treatment discontinuation may be considered as follows:
In HBe Ag positive patient's treatment should be administered

- for at least 6-12 months after confirmed HBe seroconversion (i.e HBeAGg loss and HBV DNA loss with anti-HBe detection)or
- until HBs seroconversion or
- until loss of efficacy (see section 4.4)

Serum ALT and HBV DNA levels should be followed regularly after treatment discontinuation to detect any late virological relapse.
In HBe Ag negative patient's treatment should be administered

- at least until HB seroconversion or
- until there is evidence of loss of efficacy

With prolonged treatment for more than 2 years, regular reassessment is recommended to confirm that continuing the selected therapy remains appropriate for the patient.

Paediatric patients: Texavir is not recommended for use in children and adolescents below the age of 18 years due to insufficient data on safety and efficacy (see section 5.1)

Elderly: No data are available on which to make a dose recommendation for patients over the age of 65 years (see section 4.4)

Renal impairment:
Mild renal impairment: No dose adjustment is necessary for patients with mild renal impairment (creatinine clearance 50-80 ml/min). Long-term safety data are not available for this population.
Routine monitoring of calculated creatinine clearance and serum phosphate should be performed in patients with mild renal impairment (see section 4.4).
Moderate to severe renal impairment: Significantly increased drug exposures occurred when tenofovir was administered to patients with moderate to severe renal impairment (see section 5.2). Therefore, the dosing interval of Texavir should be adjusted in patients with baseline creatinine clearance <50ml/min using the recommendations in the below table. These dosing interval recommendations are based on modeling of single-dose pharmacokinetic data in non-HIV and non-HBV infected subjects with varying degrees of renal impairment , including end-stage renal disease requiring haemodialysis . The safety and effectiveness of these dosing interval adjustment recommendations have not been clinically evaluated in patients with moderate or severe renal impairment; therefore clinical response to treatment and renal function should be closely monitored in these patients (see section 4.4).

Table 1: Dosage Adjustment for patients with Altered Creatinine Clearance

	Creatinine Clearance (ml/min)*			
	≥50	**30-49**	**10-29***	Haemodialysis
Recommended Dosing Interval (300 mg tenofovir disoproxil fumarate)	Every 24 hours	Every 48 hours	Every 72 to 96 hours	Every 7days or after a total of approximately 12 hours of dialysis +

*Calculated using ideal (lean) body weight
Adequate dose adjustments cannot be applied due to lack of alternative tablet strengths, therefore use in this group of patients is generally not recommended. If no alternative treatment is available, prolonged dose intervals may be used as detailed herein.
+Generally once weekly assuming three haemodialysis sessions a week of approximately 4 hours duration. Tenofovir disoproxil fumarate 300mg Tablets should be administered following completion of dialysis.

The pharmacokinetics of tenofovir have not been evaluated in non-haemodialysis patients with Creatinine Clearance<10ml/min; therefore, no dosing recommendation is available for these patients.
Hepatic impairment: No dose requirement is required in patients with hepatic impairment (see section 4.4 and 5.2).

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

Discontinuation of therapy:
If Texavir 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 (see section 4.4).

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warning and special precautions for use
General: Tenofovir disoproxil fumarate has not been studied in patients under 18 years or in patients over the age of 65years. Elderly patients are more likely to have decreased renal function, therefore caution should be exercised when treating elderly patients with tenofovir disoproxil fumarate (see below).

HIV antibody testing should be offered to all HBV infected patients before initiating tenofovir therapy (see below *Co-infection with HIV -1 and hepatitis B*). In turn, 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
Texavir should not be administered with any other medicinal products containing tenofovir disoproxil fumarate or adefovir dipivoxil.

Co-administration of tenofovir disoproxil fumarate and didanosine is not recommended. Co-administration of tenofovir disoproxil fumarate and didanosine may increase the risk of didanosine-related adverse events (see section 4.5). Rare cases of pancreatitis and lactic acidosis, sometimes fatal, have been reported. Co-administration of tenofovir disoproxil fumarate and didanosine at a dose 400mg daily has been associated with 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 was combined with lamivudine and abacavir as well as lamivudine and didanosine.

Renal function.
Tenofovir is primarily excreted by the kidneys, through a combination of glomerular filtration and active tubular secretion. Renal failure, renal impairment, elevated creatinine , hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir disoproxil fumarate in clinical practice (see section 4.8). It is recommended that Creatinine Clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with Texavir. Routine monitoring of calculated Creatinine Clearance and serum phosphate should be performed in patients at risk for renal impairment.

There is limited data on the safety and efficacy of tenofovir disoproxil fumarate in patients with impaired renal function (<80 ml/min). Therefore, tenofovir disoproxil fumarate should only be used if the potential benefits of treatment are considered to outweight the potential risks. Dose interval adjustments are recommended for patients with Creatinine Clearance30-49 ml/min (see section 4.2). Limited clinical study data suggests that the prolonged dose interval is not optimal and could result in increased toxicity and possibly inadequate response. In patients with severe renal impairment (Creatinine Clearance< 30ml/min) use of tenofovir is generally not

recommended. If no alternative treatment is available, the dosing interval must be adjusted and renal function should be closely monitored (see sections 4.2 and 5.2).

In patients receiving, tenofovir disoproxil fumarate, if serum phosphate is <1.5 mg/dl (0.48 mmol/l)or Creatinine Clearance decreases below 50mm/min, renal function should be re-evaluated within one week , including measurements of blood glucose, blood potassium and urine glucose concentrations (see section 4.8, proximal tubulopathy). Consideration should also be given to interrupting treatment with tenofovir disoproxil fumarate in patients whose Creatinine Clearance falls below 50 ml/ or whose serum phosphate decreases below 1.0 mg/dl (0.32 mmol/l).

Use of tenofovir disoproxil fumarate should be avoided with concurrent use of a nephrotoxic medicinal product (e.g. aminoglycosides, amphotericin B, foscamel, 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 (see section 4.8). 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 diseases 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.

Liver disease: Safety and efficacy data are limited in liver transplant patients. The safety of tenofovir in patients with decompensated liver disease and who have a Child-Pugh-Turcotte (CPT) score >9 has not been thoroughly evaluated. These patients may be at higher risk of experiencing serious hepatic or renal adverse reactions. Therefore, hepatobiliary and renal parameters should be closely monitored in this patient population.

Exacerbations of hepatitis – Flares on treatment: Spontaneous exacerbations in chronic hepatitis B are relatively common and are characterized by transient increase

in serum ALT. After initiating antiviral therapy, serum ALT may increase in some patients as serum HBV DNA levels decline (see section 4.8). Among tenofovir-treated patients, on-treatment exacerbations typically occurred after 4-8 weeks of therapy. In patients with compensated liver disease, these increases in serum ALT are generally not accompanied by an increase in serum billirubin concentrations or hepatic decompensation following hepatitis exacerbation, and therefore should be monitored closely during therapy.

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

Co-infection with HIV-1 and hepatitis B: due to the risk of development of HIV resistance , tenofovir disoproxil fumarate should only be used as part of an appropriate antiretroviral combination regimen in HIV/HBV co-infected patients. 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 diseases in such patients, interruption or discontinuation of treatment should be considered. However, it should be noted that increases of ALT can be part of HBV clearance during therapy with tenofovir (see above, Flares treatment').

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, diarrhea 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 of hyperlactataemia in asymptomatic patients treated with NRTI, however, is not recommended. Symptomatic patient usually have levels >5mmol/l and require

discontinuation of all NRTI. Lactic levels >10 mmol/l usually are a medical emergency.

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 lipoatrophy 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 of physical signs of fat redistribution. Measurement of fasting serum lipids and blood glucose as well as appropriate management of lipid disorders should be considered (see section 4.8).

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), metabolic disorders (hyperlactataemia, hyperlipasemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behavior). 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 incase of relevant signs or symptoms. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

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

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

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 pathway of tenofovir, the potential for CYP450 mediated interactions involving tenofovir with other medicinal products is low.

Concomitant use not recommended:
Texavir should not be administered with any other medicinal product containing tenofovir disoproxil fumarate.

Texavir should also not be administered concurrently with adefovir dipivoxil.

Renally eliminated medicinal products: Since tenofovir is primarily eliminated by the kidneys, co-administration of tenofovir disoproxil fumarate 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.

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

Given that taccrolimus can affect renal function, close monitoring is recommeneded when it is co-administerd with tenofovir disoproxil fumarate.

Other interactions:
Interactions between tenofovir disoproxil fumarate and HIV protease inhibitors, as well as antiviral agents other than protease inhibitors, are listed in table 1 below (increased exposure is indicated as ↓ ‘’ “, no change as ↔ ‘’ “ twice daily as “b.i.d”, and once daily as ‘’q.d”).

Table 2: Interactions between tenofovir disoproxil fumarate and other medicinal products

Medicinal products by therapeutic areas (dose in mg)	**Effects on drug levels Mean % change in AUC, Cmax1 Cmin**	**Recommendation concerning co-administered with tenofovir disoproxil 300mg**
ANTI -INFECTIVES		
antiretrovirals		
Protease inhibitors		
Atazanavir (400 mgq.d.)	Atazanavir AUC ↓ 25% Cmin ↓ Cmin↓40% Tenofovir : AUC:↓24% Cmax:↓14% Cmin:↓22%	If atazanavir and tenofovir are co-administered, atazanavir should be given at the dose 300 mg q.d. together with ritonavir 100 mg q.d. (‘’rotonavir-boosting “,see below).
Atazanavir/Rotonavir (300mg/100 mg q.d.) potentiate	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 Tenofovir associated adverse events, including renal disorders. Renal function should be closely monitored (see section 4.4)
Lopinavir/Ritonavir (400 mg/100 mg b.i.d.)	Lopinavir/ritonavir: No significant effect on lopinavir/ritonavir PK parameters. Tenofovir 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 (see section 4.4) AUC: ↑32%

Medicinal products by therapeutic areas (dose in mg)	**Effects on drug levels Mean % change in AUC, Cmax1 Cmin**	**Recommendation concerning co-administered with tenofovir disoproxil 300mg**
Darunavir/ Ritonavir (300 mg/100 mg b.i.d)	Darunavir: No significant effect on darunavir/ritonavir PK parameters Tenofovir: 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 (see section 4.4)
NRTIs		
Didanosine	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 tenofovir disoproxil fumarate and didanosine is not recommended (see section 4.4).
Adefovir dipivoxil	AUC: ↔ Cmax :↔	Tenofovir disoproxil fumarate should not be administered concurrently with adefovir dipivoxil (see section 4.4)

Medicinal products by therapeutic areas (dose in mg)	Effects on drug levels Mean % change in AUC, Cmax1 Cmin	Recommendation concerning co-administered with tenofovir disoproxil 300mg
Entecavir (1 mg q.d.)	AUC: ↔ Cmax :↔	No clinically siginicant pharmacokinetic interactions when tenofovir disoproxil fumarate was co-administered with entecavir.

Studies conducted with other medicinal products: there were no clinically significant pharmacokinetic interactions when tenofovir disoproxil fumarate was co-administered with emtricitabine, lamivudine, indinavir, efavirenz, nelfinavir, saquinavir (ritonavirboosted),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 (see section 5.2).

4.6 Pregnancy and lactation

Animal studies do not indicate direct or indirect harmful effects of tenofovir disoproxil fumarate with respect to pregnancy, foetal development, parturition or postnatal development (see section 5.3). 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 (www.apregistry.com).

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

Lactation
In animal studies it has been shown that tenofovir is excreted into milk. It is not known whether tenofovir is excreted in human milk.

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 reporteded during treatment with tenofovir disoproxil fumarate.

4.8 Undesirable effects

HIV-1 and hepatitis B: In patients receiving tenofovir disoproxil fumarate, rare events of renal impairment, renal failure and proximal renal tubulopathy (including Fanconi syndrome) sometimes leading to bone abnormalities (infrequently contributing to fractures) have been reported. Monitoring of renal function is recommended for patients receiving tenofovir disoproxil fumarate (see section 4.4).

HIV-1: Assessment of adverse reactions from clinical study data is based on 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 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 at least a possible relationship to treatment are listed below by body system organ class and absolute frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥1/10) or common (≥1/100, <1/10). See also Post-marketing experience below.

Metabolism and nutrition disorders:
Very common: hypophosphataemia

Nervous system disorders:
Very common: dizziness

Gastrointestinal disorders:
Very common: diarrhea, vomiting, nausea
Common: flatulence
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 hyper- triglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia nad hyperlactataemia (see section 4.4)

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

Hepatitis B: assessment of adverse reactions from clinical study data is primarily based on experience in two double-blind comparative controlled studies in which 641 patients with chronic hepatitis B and compensated liver disease received treatment with tenofovir disoproxil fumarate300 mg daily (n=426) or adefovir dipivoxil 10 mg daily (n=215) for 48 weeks.

Adverse reactions with at least a possible causal relationship to treatment are listed below by body system organ class and frequency. Frequencies are defined as common (≥1/100,<1/10). See also Post-marketing experience below.

Nervous system disorders:
Common: headache

Gastrointestinal disorders:
Common: diarrhea, vomiting, abdominal pain, nausea, abdominal distension, flatulence

Hepatobiliary disorders:
Common: ALT increase

General disorders:
Common: fatigue

Exacerbations during treatment of hepatitis B virus: in studies of hepatitis B virus treatment in nucleoside-naïve patients, on treatment ALT elevations >10 times ULN (upper limit of normal) and >2 times baseline occurred in 2.6% of tenofovir disoproxil fumarate-treated patients versus 1.9% of adefovir dipivoxil –treated patients.

Among tenofovir disoproxil fumarate-treated patients, on treatment ALT elevations had a median time to onset of 8 weeks, resolved with continued treatment, and, in a majority of casese, were associated with a ≥2 log 10 copies/ml reductions in viral load that preceded or coincided with the ALT elevation. Periodic monitoring of hepatic function is recommended suring treatment.

Post-marketing experience: in addition to adverse reaction reports from clinical studies the following possible adverse reactions have also been identified during post-marketing safety surveillance of tenofovir disoproxil fumarate. Frequencies are defined as rare (≥1/10,000.<1/1,000) or very rare (1/10,000) including isolated reports. Because these events have been reported voluntarily from a population of unknown size, estimates of frequency cannot always be made.

Metabolism and nutrition disorders:
Rare: lactic acidosis
Not Known: hypokalaemia

Respiratory, thoracic and mediastinal disorders
Very rare: dyspnoea

Gastrointestinal:
Rare: pancreatitis

Hepatobiliary disorders:
Rare: increased transaminases
Very rare: hepatitis
Not Known: hepatic steatosis

Skin and subcutaneous tissue disorders:
Rare: rash

Musculoskeletal and connective tissue disorders:
Not known:rhabdomyolysis, osteomalacia (manifested as bone and infrequently contributing to fractures), muscular weakness, myopathy

Renal and urinary disorders:
Rare: acute renal failure, proximal renal tubulopathy (including Fanconi syndrome), increased serum creatinine
Very rare: acute tubular necrosis
Not Known: nephritis (including acute interstitial nephritis), nephrogenic diabetes insipidus

General disorders:
Very rare: asthenia
Not known: 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 casually associated with tenofovir disoproxil fumaratein the absence of proximal renal tubulopathy. In HBV infected patients,

clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of HBV therapy (see section 4.4)

4.9 Overdose

Incase overdose occurs the patient must be monitored for evidence of toxicity (see section 4.8 and 5.3), 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nucleoside and nucleotide reverse transcriptase inhibitors, ATC code: J05AF07

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 inhibits HIV-1 reverse transcriptase and the HBVpolymerase 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 αβ and ϒ. At concentrations of up to 300 μmo/l , tenofovir has also shown no effect on the synthesis of mitochondrial DNA or the production of lactic acid in *in vitro* assays.

Data pertaining to HIV
HIV antiviral activity in vitro: The concentration of tenofovir required 50% inhibition (EC50) 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 EC50 of 4.9 μmo/l in MT-4 cells.

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 ant-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.

Clinical results: In treatment naive patients, when tenofovir was combined with lamivudine and efavirenz, the proportion of patients (ITT) with HIV-RNA <50 copies/mL were 76 and 68% at 48 and 144 weeks, respectively. When tenofovir is combined with emtricitabine and efavirenz, the proportion of patients (ITT) with HIV-RNA <50 copies/mL were 80 and 64% at 48 and 144 weeks, respectively.

Data pertaining to HBV
HBV antiviral activity in vitro: The in vitro antiviral activity of tenofovir against HBV was assessed in the HepG2 2.2.15 cell line. The EC50 values for tenofovir were in range of 0.14 to 1.5 µmol/l, with CC50 (50% cytotoxicity concentration) values>100µmol/l.

Resistance: No HBV mutations associated with tenofovir disoproxil fumarate resistance have been identified in clinical traits. The risk of tenofovir resistance with longer duration therapy is presently unclear. In cell based assays, HBV strains expressing the rtV173L, rtL180M, and rtM204I/V mutations associated with resistance to entecavir showed a susceptibility to tenofovir ranging from 0.6 – to 6.9-fold that of wildtype virus. HBV strains expressing the adefovir-associated resistance mutations rtA181V and rtN236T showed a susceptibility to tenofovir ranging from 2.9- to 10-fold that of wild-type virus. Viruses containing the rt181T mutation remained susceptible to tenofovir with EC50 values 1.5-fold that of wild-type virus.
Clinical results: The demonstration of benefit of tenofovir disoproxil fumarate is based on histological, virological, biochemical and serological responses mainly in treatment-naïve adults with HBeAg positive and HBeAg negative chronic hepatitis B with compensated liver disease.

In HbeAg positive patients with compensated liver disease treated with tenofovir, 76% of randomized patients had HBV-DNA<400copies/mL (<69 IU/mL) at week 48, and 21% exhibited HbeAg seroconversion. In an open label extension of this study efficacy was maintained at 96 weeks, with 90% of patients having HBV-DNA <400 copies/ml.

When the results of these two studies were combined, response to tenofovir treatment was comparable in nucleoside-experienced and nucleoside-naïve patients and in patients with normal ALT and abnormal at baseline.

In a randomized, 48-week, double-blind, controlled study of tenofovir disoproxil fumarate in patients co-infected with HIV-1 and chronic hepatitis B with prior lamivudine experience, treatment with tenofovir was associated with a mean change in serum HBV DNA from baseline of -5.74 log10 copies/ml in the patients for whom there was 48-week data (n=18).

Co-infected with hepatitis C or D: There are no data on the efficiency of tenofovir in patients co-infected with hepatitis C or D virus.

5.2 Pharmacokinetic properties

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 Texavir in healthy volunteers, the mean (≠SD) tenofovir $Cmax$ value was 166 ng/ml (≠39) and the corresponding value for AUC was 1104 ng.h/ml (≠259). The mean tenofovir Tmax value was 1.00 hour.
The oral bioavailability of tenofovir from tenofovir disoproxil fumarate in fasted patients was approximately 25%. Administration of tenofovir disoproxil fumarate with a high fat meal enhanced the oral bioavailability, with an increase in tenofovir AUC by approximately 40% and
Cmax by approximately 14%. However, administration 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. 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 300fold) than those observed in vivo, tenofovir did not inhibit in vitro drug metabolism meditated by any of the major human CYP450 insoforms involved in drug biotransformation (CYP3A4, CYP2D6,CYP2C9,CYP2E1, or CYP1A1/2). Tenofovir disoproxil fumarate at a concentration of 100µmol/l had no effect on any of the CYP450 insoforms, 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 siginificant interactions involving tenofovir disoproxil fumarate and medicinal products metabolized by CYP450 would occur.

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 (approxiamately 300 ml/min). Renal clearance has been estimated to be approximately 160 ml/h/kg (approximately 210 ml/min), which is in excess of the glomerular filtration rate. This indicates that active tubular secretion is an important part of the elimination of tenofovir. Following oral administration the terminal half-life of tenofovir is approximately 12 to 18 hours. Studies have established the pathway of active tubular secretion of tenofovir to be influx into proximal tubule cell by the human organic anion transporters (hOAT) 1 and 3 and influx into the urine by the multidrug resistant protein 4 (MRP 4). In vitro studies have determined that neither tenofovir disoproxil fumarate nor tenofovir substrates for the CYP450 enzymes.

Age and gender

Limited data on pharmacokinetics of tenofovir in women indicates no major gender effect. Pharmacokinetics 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/mm; moderate with CrCl= 30-40 ml/min and severe with CrCl=10-29ml/min). Compared with patients with normal renal function, the mean (%CV) tenofovir exposure increased from 2,185 (12%) ng.h/ml and 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 Cmin levels in patients with renal impairment compared to patients with normal renal function. The clinical implications of this are unknown.

In patients with end-stage renal disease (ESRD) (CrCl<10 ml/min) requiring haemodialysis, between dialysis tenofovir concentrations substantially increased over 48 hours achieving a mean Cmax of 1,032 ng/ml and a mean AUC0-48h of 42,857ng.h/ml. It is recommended that the dosing interval for tenofovir disoproxil

fumarate 300mg is modified in patients with creatinine clearance <50 ml/min or in patients who already have ESRD and require dialysis (see section 4.2).

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

Hepatic impairment

A single 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 Cmax s=and AUC 0-00 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

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 ostemalacia (monkeys) and reduced bone mineral density (rats and dogs). Findings in the rat 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 alternations 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 in vivo mouse bone marrow micronucleus assay but was positive for inducing forward mutations in the *in vitro* L5178Y mouse lymphoma cell essay in the presence or absence of S9.

Tenofovir disoproxil fumarate was also weakly positive in an in vivo / in vitro unscheduled DNA synthesis test in primary rate 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 tumors, 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

Core tablet: corn Starch, croscarmellose sodium, lactose monohydrate, magnesium stearate, °°2910/Hypermellose 15cp, Titanium dioxide, Triacetin/Gycerol Trihydrate, FD&C#2/Indigo Carmine Aluminum Lake).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30°C. Keep the container tightly closed.

6.5 Nature and contents of container

Induction-sealed HDPE bottle fitted with screw cap and containing a silica gel desiccant and Rayon sanicol. Pack size: 30 tablets.

6.6 Special precautions for disposal

No special requirements.

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

Safe disposal instructions about the desiccant bag or its contents (silica gel) must not chewed, swallowed or torn. It should be disposed off intact.

7. Manufacturer and supplier

Quality Chemical Industries Ltd (CiplaQCIL)
Plot 1-7, 1st Ring Road, Luziral Industrial Park, P.O Box 34871,Kampala-Uganda.
Tel. +256312341100/65
info@ciplaqcil.co.ug: frontdesk@ciplaqcil.co.ug
www.ciplaqcil.co.ug

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