SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tenofovir disoproxil fumarate tablets 300 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film - coated tenofovir disoproxil fumarate tablet contains 245 mg of tenofovir disoproxil (as fumarate), equivalent to 300 mg of tenofovir disoproxil fumarate or 136 mg of tenofovir.

Excipient with known effect

Each tablets contains 110.00mg of Lactose monohydrate.

For full list of excipients see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet.

Tenofovir disoproxil fumarate tablets are white to off-white, oval shaped, biconvex, film coated tablets debossed with 'I' on one side and '36' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

HIV-1 infection: Tenofovir Disoproxil Fumarate 300mg Tablets 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 Tenofovir Disoproxil Fumarate 300mg Tablets to treat antiretroviral experienced patients with HIV-1 infection should be based on individual viral resistance testing and/or the treatment history of the patient.

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

Hepatitis B infection: Tenofovir Disoproxil Fumarate 300mg Tablets is indicated for 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 the treatment of HIV and for the treatment of chronic hepatitis B is 300 mg 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 HBeAg positive patients treatment should be administered

- for at least 6-12 months after confirmed HBe seroconversion (i.e. HBeAg 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 HBeAg negative patients treatment should be administered

- at least until HBs 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: Tenofovir Disoproxil Fumarate 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 (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 Tenofovir Disoproxil Fumarate 300mg Tablets should be adjusted in patients

with baseline creatinine clearance <50 ml/min using the recommendations in the below table. These dosing interval recommendations are based on modelling 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 Patients**
Recommended Dosing Interval (300 mg tenofovir disoproxil fumarate)	Every 24 hours	Every 24 hours	Every 72 to 96 hours	Every 7 days 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 <10 ml/ min; therefore, no dosing recommendation is available for these patients.

Hepatic impairment: No dose adjustment is required in patients with hepatic impairment (see sections 4.4 and 5.2).

In exceptional circumstances, in patients having particular difficulty in swallowing, Tenofovir Disoproxil Fumarate 300mg Tablets can be administered following disintegration of the tablet in at least 100 ml of water, orange juice or grape juice.

Discontinuation of therapy:

If Tenofovir Disoproxil Fumarate 300mg Tablets is discontinued in patients with chronic hepatitis B (with or without HIV coinfection), 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 warnings and special precautions for use

General: Tenofovir disoproxil fumarate has not been studied in patients under the age of 18 years or in patients over the age of 65 years. 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 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

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

There are 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 outweigh the potential risks. Dose interval adjustments are recommended for patients with creatinine clearance 30-49 ml/ min (see section 4.2). Limited clinical study data suggest 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 < 30 ml/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 50 ml/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/min 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, 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 (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-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.

Liver disease: Safety and efficacy data are very 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 characterised by transient increases 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 bilirubin concentrations or hepatic decompensation. Patients with cirrhosis may be at a higher risk for hepatic decompensation following hepatitis exacerbation, and therefore should be monitored closely during therapy.

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 exacerbations, including fatalities, have been reported. Hepatic function should be monitored at repeated intervals with both clinical and laboratory follow-up for at least 6 months after discontinuation of hepatitis B therapy. If appropriate, resumption of hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation. Liver flares are especially serious, and sometimes fatal, in patients with decompensated liver disease.

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 disease in such patients, interruption or discontinuation of treatment must be considered. However, it should be noted that increases of ALT can be part of HBV clearance during therapy with tenofovir (see above, Flares on 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, diarrhoea and abdominal pain. Risk factors for NRTIrelated 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.

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

Immune Reactivation Syndrome: in HIV-infected patients with pre-existing severe immune deficiency, typically in the first few weeks or months after initiation of combination ART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens (e.g. CMV retinitis, mycobacterial infections, 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:

Tenofovir Disoproxil Fumarate 300mg Tablets should not be administered with any other medicinal products containing tenofovir disoproxil fumarate.

Tenofovir Disoproxil Fumarate 300mg Tablets should also not be administered concurrently with adefovir dipivoxil.

Didanosine: Co-administration of tenofovir disoproxil fumarate and didanosine is not recommended (see section 4.4 and Table 2).

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.

Use of 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 (see section 4.4).

Given that tacrolimus can affect renal function, close monitoring is recommended when it is co- administered 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 "↑", decreased exposure 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, Cmax, Cmin**	**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 tenofovir are coadministered, atazanavir should be given at the dose 300 mg q.d. together with ritonavir 100 mg q.d. ("ritonavirboosting", see below).
Atazanavir/Ritonavir (300 mg/100 mg q.d.)	Atazanavir: AUC: ↓ 25% Cmax: ↓ 28% Cmin: ↓ 26%	No dose adjustment is recommended. The increased exposure of

	Tenofovir: AUC: ↑ 37% Cmax: ↑ 34% Cmin: ↑ 29%	tenofovir could potentiate 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: 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 (see section 4.4).
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 (see section 4.4).
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 coadministration. Also didanosine at 250 mg coadministered 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).
Entecavir (1 mg q.d.)	AUC: ↔ Cmax: ↔	No clinically significant pharmacokinetic interactions when tenofovir disoproxil fumarate was coadministered 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 (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 (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 therisk of overall birth defects. No increase in birth defects was seen (www.apregistry.com).

Tenofovir disoproxil fumarate should be used during pregnancy only 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 reported during treatment with tenofovir disoproxil fumarate.

4.8 Undesirable effects

HIV1 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.

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: diarrhoea, 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 and hyperlactataemia (see section 4.4).

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 intraabdominal 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 fumarate 300 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: diarrhoea, 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, ontreatment 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 dipivoxiltreated patients.

Among tenofovir disoproxil fumarate-treated patients, ontreatment ALT elevations had a median time to onset of 8 weeks, resolved with continued treatment, and, in a majority of cases, were associated with a ≥ 2 log10 copies/ml reduction in viral load that preceded or coincided with the ALT elevation. Periodic monitoring of hepatic function is recommended during 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 disorders:

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 pain and infrequently contributing to fractures), muscular weakness, myopathy

Renal and urinary disorders:

Rare: acute renal failure, 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 causally associated with tenofovir disoproxil fumarate therapy in 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).

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via the pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org.

4.9 Overdose

If overdose occurs the patient must be monitored for evidence of toxicity (see sections 4.8 and 5.3), and standard supportive treatment applied as necessary. 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, an obligate chain terminator, by constitutively expressed cellular enzymes. Tenofovir diphosphate inhibits HIV-1 reverse transcriptase and the HBV polymerase 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. 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.

Data pertaining to HIV

HIV antiviral activity in vitro: The concentration of tenofovir required for 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 µmol/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 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.

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 was 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 the range of 0.14 to 1.5 µmol/l, with CC50 (50% cytotoxicity concentration) values > 100 µmol/l.

Resistance: No HBV mutations associated with tenofovir disoproxil fumarate resistance have been identified in clinical trials. 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 lamivudine and telbivudine showed a susceptibility to tenofovir ranging from 0.7- to 3.4-fold that of wild-type virus. HBV strains expressing the rtL180M, rtT184G, rtS202G/I, rtM204V and rtM250V 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 rtA181T mutation remained susceptible to tenofovir with EC50 values 1.5-foldthat 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 randomised patients had HBV-DNA <400 copies/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 76% of patients having HBVDNA <400 copies/ml

In HbeAg negative patients with compensated liver disease treated with tenofovir, 93% of randomised patients had HBV-DNA <400 copies/mL at week 48. 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 ALT 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-infection with hepatitis C or D: There are no data on the efficacy 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 Tenofovir Disoproxil Fumarate 300mg Tablets in healthy volunteers, the mean (±SD) tenofovir Cmax value was 320 ng/ml (±145) and the corresponding value for AUC was 3295 ng.h/ml (±1050). The mean (±SD) tenofovir Tmax value was 1.89 hour (± 0.98).

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 25µg/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 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, both by filtration and an active tubular transport system with approximately 70-80% of the dose excreted unchanged in urine following intravenous administration. Total clearance has been estimated to be approximately 230 ml/h/kg (approximately 300 ml/min). Renal clearance has been estimated to be approximately 160 ml/h/kg (approximately 210 ml/min), which is in excess of the glomerular filtration rate. This indicates that active tubular secretion is an important part of the elimination of tenofovir. Following oral administration the terminal half-life 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 Cmin levels in patients with renal impairment compared with patients with normal renal function. The clinical implications of this are unknown.

In patients with end-stage renal disease (ESRD) (CrCl < 10 ml/min) requiring haemodialysis, between dialysis tenofovir concentrations substantially increased over 48 hours achieving a mean Cmax of 1,032 ng/ml and a mean AUC0-48h of 42,857 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 (see section 4.2).

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

Hepatic impairment

A single 300 mg dose of tenofovir disoproxil fumarate was administered to non-HIV, non-HBV infected patients with varying degrees of hepatic impairment defined according to Child-Pugh- Turcotte (CPT) classification. Tenofovir pharmacokineticparameters were not substantially altered in subjects with hepatic impairment suggesting that no dose adjustment is required in these subjects. The mean (%CV) tenofovir Cmax and AUC0- ∞ 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 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

Croscarmellose Sodium,

Lactose Monohydrate,

Microcrystalline Cellulose,

Pregelatinized Starch,

Magnesium Stearate,

Hypromellose,

Titanium Dioxide

Triacetin.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

HDPE container containing 30 Tablets.

6.6 Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

AUROBINDO PHARMA LTD UNIT III

SURVEY NO.313 & 31 BACHUPALLY VILLAGE

QUTHUBULLAPUR MANDAL RANGA REDDY DIST,

TELANGANA STATE INDIA

8. Marketing authorisation number
H2015/CTD3023/509/R1

9. Date of first authorisation/renewal of the authorization
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10. Date of revision of the text:
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