RICOVIR™ 75065042

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For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

℞ Tenofovir Disoproxil Fumarate Tablets IP 300 mg RICOVIR™

Label claim

Each film coated tablet contains:

Tenofovir disoproxil fumarate IP 300 mg

Colours: Titanium dioxide and Lake of Indigo Carmine

List of Excipients:

Lactose monohydrate, Magnesium stearate, Microcrystalline cellulose, Croscarmellose sodium, film coat {Lactose monohydrate, Hypromellose, Titanium dioxide, Triacetin /Glycerol triacetate, FD&C Blue #2 / Lake of Indigo carmine.

Therapeutic indications

Tenofovir disoproxil fumarate Tablet is indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected adults.

HIV-1 infection

The demonstration of the benefit of Tenofovir disoproxil fumarate Tablet in HIV-1 infection is based on results of one study in treatment-naïve patients, including patients with a high viral load (> 100,000 copies/ml) and studies in which Tenofovir disoproxil fumarate Tablet was added to stable background therapy (mainly tritherapy) in antiretroviral pre-treated patients experiencing early virological failure (< 10,000 copies/ml, with the majority of patients having < 5,000 copies/ml).

The choice of Tenofovir disoproxil fumarate to treat antiretroviral experienced patients should be based on individual viral resistance testing and/or treatment history of patients.

Hepatitis B infection

Tenofovir disoproxil fumarate Tablet 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

• decompensated liver disease

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 of Tenofovir disoproxil fumarate Tablet for the treatment of HIV or for the treatment of chronic hepatitis B is 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 without cirrhosis, treatment should be administered for at least 6-12 months after HBe seroconversion (HBeAg loss and HBV DNA loss with anti-HBe detection) is confirmed or until HBs seroconversion or there is loss of efficacy. Serum ALT and HBV DNA levels should be followed regularly after treatment discontinuation to detect any late virological relapse.

- In HBeAg negative patients without cirrhosis, treatment should be administered at least until HBs seroconversion or 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.

If a patient misses a dose of Tenofovir disoproxil fumarate Tablet within 12 hours of the time it is usually taken, the patient should take Tenofovir disoproxil fumarate Tablet with food as soon as possible and resume their normal dosing schedule. If a patient misses a dose of Tenofovir disoproxil fumarate Tablet by more than 12 hours and it is almost time for their next dose, the patient should not take the missed dose and simply resume the usual dosing schedule.

If the patient vomits within 1 hour of taking Tenofovir disoproxil fumarate Tablet, another tablet should be taken. If the patient vomits more than 1 hour after taking Tenofovir disoproxil fumarate Tablet they do not need to take another dose.

Special populations

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

Renal insufficiency: Tenofovir is eliminated by renal excretion and the exposure to tenofovir increases in patients with renal dysfunction. There are limited data on the safety and efficacy of tenofovir disoproxil fumarate in patients with moderate and severe renal impairment (creatinine clearance < 50 ml/min) and long-term safety data has not been evaluated for mild renal impairment (creatinine clearance 50-80 ml/min). Therefore, in patients with renal impairment tenofovir disoproxil fumarate should only be used if the potential benefits of treatment are considered to outweigh the potential risks. Dosing interval adjustment is required in all patients with creatinine clearance < 50 ml/min.

Mild renal impairment (creatinine clearance 50-80 ml/min): Limited data from clinical studies support once daily dosing of tenofovir disoproxil fumarate in patients with mild renal impairment.

Moderate renal impairment (creatinine clearance 30-49 ml/min): Administration of tenofovir disoproxil (as fumarate) every 48 hours is recommended 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, but has not been confirmed in clinical studies. Therefore, clinical response to treatment and renal function should be closely monitored in these patients.

Severe renal impairment (creatinine clearance < 30 ml/min) and haemodialysis patients: Adequate dose adjustments cannot be applied due to lack of alternative tablet strengths, therefore use in this group of patients is not recommended. If no alternative treatment is available, prolonged dose intervals may be used as follows:

Severe renal impairment: Tenofovir disoproxil (as fumarate) may be administered every 72-96 hours (dosing twice a week).

Haemodialysis patients: Tenofovir disoproxil (as fumarate) may be administered every 7 days following completion of a haemodialysis session*.

These dose adjustments have not been confirmed in clinical studies. Simulations suggest that the prolonged dose interval is not optimal and could result in increased toxicity and possibly inadequate response. Therefore clinical response to treatment and renal function should be closely monitored.

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

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

Hepatic impairment: No dose adjustment is required in patients with hepatic impairment.

If Tenofovir disoproxil fumarate Tablet is discontinued in patients with chronic hepatitis B with or without HIV co-infection, these patients should be closely monitored for evidence of exacerbation of hepatitis.

Paediatric population: Tenofovir disoproxil fumarate Tablet is not recommended for use in children.

The clinical data available in HIV-1 infected adolescents are inadequate to support the use of tenofovir disoproxil fumarate in this population and no data are currently available in younger children.

No data are currently available in paediatric patients infected with chronic hepatitis B.

Method of administration

Tenofovir disoproxil fumarate Tablet tablets should be taken once daily, orally with food.

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

Contraindications

Known hypersensitivity to the active substance or to any of the excipients.

Special warning and precautions for use

General: HIV antibody testing should be offered to all HBV infected patients before initiating tenofovir disoproxil fumarate therapy (*see below Co-infection with HIV-1 and hepatitis B*).

Patients must be advised that tenofovir disoproxil fumarate has not been proven to prevent the risk of transmission of HIV or HBV to others through sexual contact or contamination with blood. Appropriate precautions must continue to be used.

Tenofovir disoproxil fumarate Tablet contains lactose monohydrate. Consequently, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

Co-administration of other medicinal products:

- Tenofovir disoproxil fumarate Tablet should not be administered concomitantly with other medicinal products containing tenofovir disoproxil fumarate.
- Tenofovir disoproxil fumarate Tablet should not be administered concomitantly with adefovir dipivoxil.
- Co-administration of tenofovir disoproxil fumarate and didanosine is not recommended. Co-administration of tenofovir disoproxil fumarate and didanosine results in a 40-60% increase in systemic exposure to didanosine that may increase the risk of didanosine-related adverse reactions. Rarely, 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 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 an early stage in HIV patients when tenofovir disoproxil fumarate was combined with lamivudine and abacavir as well as with lamivudine and didanosine as a once daily regimen.

Renal Impairment: Tenofovir is principally eliminated via the kidney. 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.

Renal safety with tenofovir has only been studied to a very limited degree in patients with impaired renal function (creatinine clearance < 80 ml/min).

It is recommended that creatinine clearance is calculated in all patients prior to initiating therapy with tenofovir disoproxil fumarate and renal function (creatinine clearance and serum phosphate) is also monitored every four weeks during the first year, and then every three months. In patients at risk for renal impairment, including patients who have previously experienced renal events while receiving adefovir dipivoxil, consideration should be given to more frequent monitoring of renal function.

Patients with creatinine clearance < 50 ml/min, including haemodialysis patients: There are limited data on the safety and efficacy of tenofovir disoproxil fumarate in patients with impaired renal function. Therefore, tenofovir disoproxil fumarate should only be used if the potential benefits of treatment are considered to outweigh the potential risks. In patients with severe renal impairment (creatinine clearance < 30 ml/min) and in patients who require haemodialysis use of tenofovir is not recommended. If no alternative treatment is available, the dosing interval must be adjusted and renal function should be closely monitored

If serum phosphate is < 1.5 mg/dl (0.48 mmol/l) or creatinine clearance is decreased to < 50 ml/min, renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations, and the dose interval of Tenofovir disoproxil fumarate adjusted. Consideration should also be given to interrupting treatment with tenofovir disoproxil fumarate in patients with creatinine clearance decreased to < 50 ml/min or decreases in serum phosphate to < 1.0 mg/dl (0.32 mmol/l).

Use of tenofovir disoproxil fumarate should be avoided with concurrent or recent 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.

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

Bone effects: In HIV infected patients, in a 144-week controlled clinical study that compared tenofovir disoproxil fumarate with stavudine in combination with lamivudine and efavirenz in antiretroviral-naïve patients, small decreases in bone mineral density of the hip and spine were observed in both treatment groups. Decreases in BMD of spine and changes in bone biomarkers from baseline were significantly greater in the tenofovir disoproxil fumarate treatment group at 144 weeks. Decreases in BMD 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 or detected then appropriate consultation should be obtained.

Paediatric population: Tenofovir disoproxil fumarate Tablet may cause a reduction in BMD. The effects of tenofovir disoproxil fumarate-associated changes in BMD on long-term bone health and future fracture risk are currently unknown.

Liver disease: Safety and efficacy data are very limited in liver transplant patients.

There are limited data on the safety and efficacy of tenofovir disoproxil fumarate in HBV infected patients with decompensated liver disease and who have a Child-Pugh-Turcotte (CPT) score > 9. 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. In patients with compensated liver disease, these increases in serum ALT are generally not accompanied by an increase in serum bilirubin concentrations or hepatic decompensation. Patients with cirrhosis may be at a higher risk for hepatic decompensation following hepatitis exacerbation, and therefore should be monitored closely during therapy.

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

Liver flares are especially serious, and sometimes fatal in patients with decompensated liver disease.

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.

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 Exacerbations of hepatitis.

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

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

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

Patients at increased risk should be followed closely.

Lipodystrophy: Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors and lipoatrophy and nucleoside reverse transcriptase inhibitors has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

Tenofovir is structurally related to nucleoside analogues hence the risk of lipodystrophy cannot be excluded. However, 144-week clinical data from antiretroviral-naïve patients indicate that the risk of lipodystrophy was lower with tenofovir disoproxil fumarate than with stavudine when administered with lamivudine and efavirenz.

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 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 recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

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

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

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

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 Tablet should not be administered concomitantly with other medicinal products containing tenofovir disoproxil fumarate.

Tenofovir disoproxil fumarate Tablet should not be administered concomitantly with adefovir dipivoxil.

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.

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

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 protease inhibitors and antiretroviral agents other than protease inhibitors are listed in Table 1 below (increase is indicated as "↑", decrease as "↓", no change as "↔", twice daily as "b.i.d.", and once daily as "q.d.").

Table 1: Interactions between tenofovir disoproxil Fumarate and other medicinal products

Medicinal product by therapeutic areas (dose in mg)	Effects on drug levels Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with tenofovir disoproxil fumarate 300 mg
ANTI-INFECTIVES		
Antiretrovirals		
Protease inhibitors		
Atazanavir/Ritonavir (300 q.d./100 q.d./300 q.d.)	Atazanavir: AUC: ↓ 25% C_{max}: ↓ 28% C_{min}: ↓ 26% Tenofovir: AUC: ↑ 37% C_{max}: ↑ 34% C_{min}: ↑ 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 b.i.d./100 b.i.d./300 q.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 (300/100 b.i.d./300 q.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	Co-administration of tenofovir disoproxil fumarate and didanosine results in a 40-60% increase in systemic exposure to didanosine that may increase the risk for didanosine-related adverse reactions. Rarely, 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 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.	Co-administration of tenofovir disoproxil fumarate and didanosine is not recommended.
Adefovir dipivoxil	AUC: ↔ C_{max}: ↔	Tenofovir disoproxil fumarate should not be administered concurrently with adefovir dipivoxil.
Entecavir	AUC: ↔ C_{max}: ↔	No clinically significant 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 (ritonavir boosted), methadone, ribavirin, rifampicin, tacrolimus, or the hormonal contraceptive norgestimate/ethinyl oestradiol.

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

Fertility, Pregnancy and lactation

Pregnancy

A moderate amount of data on pregnant women (between 300-1,000 pregnancy outcomes) indicate no malformations or foetal/neonatal toxicity associated with tenofovir disoproxil fumarate. Animal studies do not indicate reproductive toxicity. The use of tenofovir disoproxil fumarate may be considered during pregnancy, if necessary..

Lactation

Tenofovir has been shown to be excreted in human milk. There is insufficient information on the effects of tenofovir in newborns/infants. Therefore Tenofovir disoproxil fumarate Tablet should not be used during breast-feeding.

As a general rule, it is recommended that HIV and HBV infected women do not breast-feed their infants in order to avoid transmission of HIV and HBV to the infant.

Fertility

There are limited clinical data with respect to the effect of tenofovir disoproxil fumarate on fertility. Animal studies do not indicate harmful effects of tenofovir disoproxil fumarate on fertility.

Effects on ability to drive and use machines

No studies on the effects on 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.

Undesirable effects

a. Summary of the safety profile

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 Tablet.

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

Lactic acidosis, severe hepatomegaly with steatosis and lipodystrophy are associated with tenofovir disoproxil fumarate.

Co-administration of Tenofovir Disoproxil Fumarate and didanosine is not recommended as this may result in an increased risk of adverse reactions. Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported.

Hepatitis B: Approximately one quarter of patients can be expected to experience adverse reactions following treatment with tenofovir disoproxil fumarate, most of which are mild. In clinical trials of HBV infected patients, the most frequently occurring adverse reaction to tenofovir disoproxil fumarate was nausea (5.4%).

Acute exacerbation of hepatitis has been reported in patients on treatment as well as in patients who have discontinued hepatitis B therapy.

b. Tabulated summary of adverse reactions

Assessment of adverse reactions for tenofovir disoproxil fumarate is based on safety data from clinical studies and post-marketing experience. All adverse reactions are presented in Table 2.

HIV-1 clinical studies: Assessment of adverse reactions is based on post-marketing experience and experience in two studies in 653 treatment-experienced patients receiving treatment with tenofovir disoproxil fumarate (n = 443) or placebo (n = 210) in combination with other antiretroviral medicinal products for 24 weeks and also in a double-blind comparative controlled study in which 600 treatment-naïve patients received treatment with tenofovir disoproxil 245 mg (as fumarate) (n = 299) or stavudine (n = 301) in combination with lamivudine and efavirenz for 144 weeks.

Hepatitis B clinical studies: Assessment of adverse reactions from HBV 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 245 mg (as fumarate) daily (n = 426) or adefovir dipivoxil 10 mg daily (n = 215) for 48 weeks The adverse reactions observed with continued treatment for 240 weeks were consistent with the safety profile of tenofovir disoproxil fumarate.

Patients with decompensated liver disease: The safety profile of tenofovir disoproxil fumarate in patients with decompensated liver disease was assessed in a double-blind active controlled study (GS-US-174-0108) in which patients received treatment with tenofovir disoproxil fumarate (n = 45) or emtricitabine plus tenofovir disoproxil fumarate (n = 45) or entecavir (n = 22) for 48 weeks.

In the tenofovir disoproxil fumarate treatment arm, 7% of patients discontinued treatment due to an adverse event; 9% of patients experienced a confirmed increase in serum creatinine of 0.5 mg/dl or confirmed serum phosphate of < 2 mg/dl through week 48; there were no statistically significant differences between the combined tenofovir-containing arms and the entecavir arm. Subjects with a high baseline CPT score were at higher risk of developing serious adverse events.

Hepatocellular carcinoma was diagnosed in 3 patients in the tenofovir disoproxil fumarate group and two patients in the tenofovir disoproxil fumarate group died during the study.

The adverse reactions with suspected (at least 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), common (1/100 to < 1/10), uncommon (1/1000 to < 1/100) or rare (1/10,000 to < 1/1000).

Table 2: Tabulated summary of adverse reactions associated with tenofovir disoproxil fumarate based on clinical study and post-marketing experience

Frequency	Tenofovir disoproxil fumarate
Metabolism and nutrition disorders:	
Very common:	hypophosphataemia[1]
Uncommon:	hypokalaemia[1]
Rare:	lactic acidosis[3]
Nervous system disorders:	
Very common:	dizziness
Common:	headache
Gastrointestinal disorders:	
Very common:	diarrhoea, nausea, vomiting
Common:	abdominal pain, abdominal distension, flatulence
Uncommon:	pancreatitis[3]
Hepatobiliary disorders:	
Common:	increased transaminases
Rare:	hepatic steatosis[3], hepatitis
Skin and subcutaneous tissue disorders:	
Very common:	rash
Rare:	angioedema
Musculoskeletal and connective tissue disorders:	
Uncommon:	rhabdomyolysis[1], muscular weakness[1]
Rare:	myopathy[1], osteomalacia (manifested as bone pain and infrequently contributing to fractures)[1, 2],
Renal and urinary disorders:	
Uncommon:	increased creatinine
Rare:	acute renal failure, renal failure, acute tubular necrosis, proximal renal tubulopathy (including Fanconi syndrome), nephritis (including acute interstitial nephritis)[2], nephrogenic diabetes insipidus
General disorders and administration site conditions:	
Very common:	asthenia
Common:	fatigue

[1] This adverse reaction may occur as a consequence of proximal renal tubulopathy. It is not considered to be causally associated with tenofovir disoproxil fumarate in the absence of this condition.

[2] This adverse reaction was identified through post-marketing surveillance but not observed in randomised controlled clinical trials or the tenofovir disoproxil fumarate expanded access program. The frequency category was estimated from a statistical calculation based on the total number of patients exposed to tenofovir disoproxil fumarate in randomised controlled clinical trials and the expanded access program (n = 7,319).

[3] See section c. Description of selected adverse reactions for more details.

c. Description of selected adverse reactions

HIV-1 and hepatitis B:

Renal impairment: As Tenofovir Disoproxil Fumarate Tablet may cause renal damage monitoring of renal function is recommended.

HIV-1:

Interaction with didanosine: Co-administration of tenofovir disoproxil fumarate and didanosine is not recommended as it results in a 40-60% increase in systemic exposure to didanosine that may increase the risk of didanosine-related adverse reactions. Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported.

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

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

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

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			Date of Return		
[ ] New Component			Material Code	75065042 Supersedes 75055063	Market MYLAN-INDIA
[ ] Immediately (Stock of superseded component to be destroyed, if applicable.)			Description	LIT. RICOVIR TABS 300 mg MYLAN-INDIA V3	
[ ] After consumption of existing (superseded) stock.			Component	Printed Literature	Actual Size Flat - 272 x 470 mm; Folded - 34 x 56 mm
[ ] Other (Specify)			Substrate	50 gsm Century Maplitho Paper	
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			Design & Style	Supply Leaflet in folded form as Proposed Size (with tape)	
			Reason for Issue	A/w updated as per Gazette Guideline and Folding Size	
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mean increases in fasting triglycerides and total cholesterol than the comparator arm.

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

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

Lactic acidosis and severe hepatomegaly with steatosis: Lactic acidosis, usually associated with hepatic steatosis, has been reported with the use of nucleoside analogues. Treatment with nucleoside analogues should be discontinued in the setting of symptomatic hyperlactataemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.

Hepatitis B:

Exacerbations of hepatitis during treatment: In studies with 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. 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 log_{10} copies/ml reduction in viral load that preceded or coincided with the ALT elevation. Periodic monitoring of hepatic function is recommended during treatment.

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

d. Paediatric population

Assessment of adverse reactions is based on one randomised trial (study GS-US-104-0321) in 87 HIV-1 infected adolescent patients (aged 12 to < 18 years) who received treatment with tenofovir disoproxil fumarate (n = 45) or placebo (n = 42) in combination with other antiretroviral agents for 48 weeks.

e. Other special population(s)

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

Patients with renal impairment: Since tenofovir disoproxil fumarate can cause renal toxicity, close monitoring of renal function is recommended in any patient with renal impairment treated with Tenofovir Disoproxil Fumarate Tablet.

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. It is not known whether tenofovir can be removed by peritoneal dialysis.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Antiviral for systemic use ; nucleoside and nucleotide reverse transcriptase inhibitors, ATC code: J05AF07

Mechanism of action and pharmacodynamic effects: 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 has an intracellular half-life of 10 hours in activated and 50 hours in resting peripheral blood mononuclear cells (PBMCs). Tenofovir diphosphate inhibits viral polymerases by direct binding competition with the natural deoxyribonucleotide substrate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of cellular polymerases α, β, and γ. At concentrations of up to 300 μ mol/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 (EC_{50}) of the wild-type laboratory strain HIV-1IIIB is 1-6 µmol/l in lymphoid cell lines and 1.1 µmol/l against primary HIV-1 subtype B isolates in PBMCs. Tenofovir is also active against HIV-1 subtypes A, C, D, E, F, G, and O and against HIV_{BaL} in primary monocyte/macrophage cells. Tenofovir shows activity *in vitro* against HIV-2, with an EC_{50} of 4.9 µmol/l in MT-4 cells.

Resistance: Strains of HIV-1 with reduced susceptibility to tenofovir and a K65R mutation in reverse transcriptase have been selected in vitro and in some patients (see Clinical results). Tenofovir disoproxil fumarate should be avoided in antiretroviral experienced patients with strains harbouring the K65R mutation.

Clinical studies in treatment-experienced patients have assessed the anti-HIV activity of tenofovir disoproxil 245 mg (as fumarate) against strains of HIV-1 with resistance to nucleoside inhibitors. The results indicate that patients whose HIV expressed 3 or more thymidine-analogue associated mutations (TAMs) that included either the M41L or L210W reverse transcriptase mutation showed reduced response to tenofovir disoproxil 245 mg (as fumarate) therapy.

Clinical efficacy and safety: The effects of tenofovir disoproxil fumarate in treatment-experienced and treatment-naïve HIV-1 infected adults have been demonstrated in trials of 48 weeks and 144 weeks duration, respectively.

In study GS-99-907, 550 treatment-experienced patients were treated with placebo or tenofovir disoproxil 245 mg (as fumarate) for 24 weeks. The mean baseline CD4 cell count was 427 cells/mm3, the mean baseline plasma HIV-1 RNA was 3.4 log_{10} copies/ml (78% of patients had a viral load of < 5,000 copies/ml) and the mean duration of prior HIV treatment was 5.4 years. Baseline genotypic analysis of HIV isolates from 253 patients revealed that 94% of patients had HIV-1 resistance mutations associated with nucleoside reverse transcriptase inhibitors, 58% had mutations associated with protease inhibitors and 48% had mutations associated with non-nucleoside reverse transcriptase inhibitors.

At week 24 the time-weighted average change from baseline in log10 plasma HIV-1 RNA levels (DAVG24) was -0.03 log_{10} copies/ml and -0.61 log_{10} copies/ml for the placebo and tenofovir disoproxil 245 mg (as fumarate) recipients (p < 0.0001). A statistically significant difference in favour of tenofovir disoproxil 245 mg (as fumarate) was seen in the time-weighted average change from baseline at week 24 (DAVG24) for CD4 count (+13 cells/mm³ for tenofovir disoproxil 245 mg (as fumarate) versus -11 cells/mm3 for placebo, p-value = 0.0008). The antiviral response to tenofovir disoproxil fumarate was durable through 48 weeks (DAVG48 was -0.57 log_{10} copies/ml, proportion of patients with HIV-1 RNA below 400 or 50 copies/ml was 41% and 18% respectively). Eight (2%) tenofovir disoproxil 245 mg (as fumarate) treated patients developed the K65R mutation within the first 48 weeks.

The 144-week, double-blind, active controlled phase of study GS-99-903 evaluated the efficacy and safety of tenofovir disoproxil 245 mg (as fumarate) versus stavudine when used in combination with lamivudine and efavirenz in HIV-1 infected patients naïve to antiretroviral therapy. The mean baseline CD4 cell count was 279 cells/mm³, the mean baseline plasma HIV-1 RNA was 4.91 log_{10} copies/ml, 19% of patients had symptomatic HIV-1 infection and 18% had AIDS. Patients were stratified by baseline HIV-1 RNA and CD4 count. Forty-three percent of patients had baseline viral loads > 100,000 copies/ml and 39% had CD4 cell counts < 200 cells/ml.

By intent to treat analysis (Missing data and switch in antiretroviral therapy (ART) considered as failure), the proportion of patients with HIV-1 RNA below 400 copies/ml and 50 copies/ml at 48 weeks of treatment was 80% and 76% respectively in the tenofovir disoproxil 245 mg (as fumarate) arm, compared to 84% and 80% in the stavudine arm. At 144 weeks, the proportion of patients with HIV-1 RNA below 400 copies/ml and 50 copies/ml was 71% and 68% respectively in the tenofovir disoproxil 245 mg (as fumarate) arm, compared to 64% and 63% in the stavudine arm.

The average change from baseline for HIV-1 RNA and CD4 count at 48 weeks of treatment was similar in both treatment groups (-3.09 and -3.09 log_{10} copies/ml; +169 and 167 cells/mm³ in the tenofovir disoproxil 245 mg (as fumarate) and stavudine groups, respectively). At 144 weeks of treatment, the average change from baseline remained similar in both treatment groups (-3.07 and -3.03 log_{10} copies/ml; +263 and +283 cells/mm³ in the tenofovir disoproxil 245 mg (as fumarate) and stavudine groups, respectively). A consistent response to treatment with tenofovir disoproxil 245 mg (as fumarate) was seen regardless of baseline HIV-1 RNA and CD4 count.

The K65R mutation occurred in a slightly higher percentage of patients in the tenofovir disoproxil fumarate group than the active control group (2.7% versus 0.7%). Efavirenz or lamivudine resistance either preceded or was coincident with the development of K65R in all cases. Eight patients had HIV that expressed K65R in the tenofovir disoproxil 245 mg (as fumarate) arm, 7 of these occurred during the first 48 weeks of treatment and the last one at week 96. No further K65R development was observed up to week 144. From both the genotypic and phenotypic analyses there was no evidence for other pathways of resistance to tenofovir.

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 EC_{50} values for tenofovir were in the range of 0.14 to 1.5 µmol/l, with CC_{50} (50% cytotoxicity concentration) values > 100 µmol/l.

Resistance: No HBV mutations associated with tenofovir disoproxil fumarate resistance have been identified (see Clinical results). 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 wild-type 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 EC_{50} values 1.5-fold that of wild-type virus.

Clinical efficacy and safety: The demonstration of benefit of tenofovir disoproxil fumarate in compensated and decompensated disease is based on virological, biochemical and serological responses in adults with HBeAg positive and HBeAg negative chronic hepatitis B. Treated patients included those who were treatment-naïve, lamivudine-experienced, adefovir dipivoxil-experienced and patients with lamivudine and/or adefovir dipivoxil resistance mutations at baseline. Benefit has also been demonstrated based on histological responses in compensated patients.

Experience in patients with compensated liver disease at 48 weeks (studies GS-US-174-0102 and GS-US-174-0103): Results through 48 weeks from two randomised, phase 3 double-blind studies comparing tenofovir disoproxil fumarate to adefovir dipivoxil in patients with compensated liver disease are presented in Table 3 below. Study GS-US-174-0103 was conducted in 266 (randomised and treated) HBeAg positive patients while study GS-US-174-0102 was conducted in 375 (randomised and treated) patients negative for HBeAg and positive for HBeAb.

In both of these studies tenofovir disoproxil fumarate was significantly superior to adefovir dipivoxil for the primary efficacy endpoint of complete response (defined as HBV DNA levels < 400 copies/ml and Knodell necroinflammatory score improvement of at least 2 points without worsening in Knodell fibrosis). Treatment with tenofovir disoproxil 245 mg (as fumarate) was also associated with significantly greater proportions of patients with HBV DNA < 400 copies/ml, when compared to adefovir dipivoxil 10 mg treatment. Both treatments produced similar results with regard to histological response (defined as Knodell necroinflammatory score improvement of at least 2 points without worsening in Knodell fibrosis) at week 48 (see Table 3 below).

In study GS-US-174-0103 a significantly greater proportion of patients in the tenofovir disoproxil fumarate group than in the adefovir dipivoxil group had normalised ALT and achieved HBsAg loss at week 48 (see Table 3 below).

Table 3: Efficacy parameters in compensated HBeAg positive and HBeAg negative patients at week 48

	Study 174-0102 (HBeAg negative)		Study 174-0103 (HBeAg positive)	
Parameter	**Tenofovir disoproxil 245 mg (as fumarate) n = 250**	**Adefovir dipivoxil 10 mg n = 125**	**Tenofovir disoproxil 245 mg (as fumarate) n = 176**	**Adefovir dipivoxil 10 mg n = 90**
Complete response (%)[a]	71*	49	67*	12
Histology Histological response (%)[b]	72	69	74	68
Median HBV DNA reduction from baseline[c] (log_{10} copies/ml)	-4.7*	-4.0	-6.4*	-3.7
HBV DNA (%) < 400 copies/ml (< 69 IU/ml)	93*	63	76*	13
ALT (%) Normalised ALT[d]	76	77	68*	54
Serology (%) HBeAg loss/seroconversion	N/A	N/A	22/21	18/18
HBsAg loss/seroconversion	0/0	0/0	3*/1	0/0

* p-value versus adefovir dipivoxil < 0.05,

[a] Complete response defined as HBV DNA levels < 400 copies/ml and Knodell necroinflammatory score improvement of at least 2 points without worsening in Knodell fibrosis,

[b] Knodell necroinflammatory score improvement of at least 2 points without worsening in Knodell fibrosis,

[c] Median change from baseline HBV DNA merely reflects the difference between baseline HBV DNA and the limit of detection (LOD) of the assay,

[d] The population used for analysis of ALT normalisation included only patients with ALT above ULN at baseline. N/A= not applicable.

Tenofovir disoproxil fumarate was associated with significantly greater proportions of patients with undetectable HBV DNA (< 169 copies/ml [< 29 IU/ml]; the limit of quantification of the Roche Cobas Taqman HBV assay), when compared to adefovir dipivoxil (study GS-US-174-0102; 91%, 56% and study GS-US-174-0103; 69%, 9%), respectively.

Response to treatment with tenofovir disoproxil fumarate was comparable in nucleoside-experienced (n = 51) and nucleoside-naïve (n = 375) patients and in patients with normal ALT (n = 21) and abnormal ALT (n = 405) at baseline when studies GS-US-174-0102 and GS-US-174-0103 were combined. Forty-nine of the 51 nucleoside-experienced patients were previously treated with lamivudine. Seventy-three percent of nucleoside-experienced and 69% of nucleoside-naïve patients achieved complete response to treatment; 90% of nucleoside-experienced and 88% of nucleoside-naïve patients achieved HBV DNA suppression < 400 copies/ml. All patients with normal ALT at baseline and 88% of patients with abnormal ALT at baseline achieved HBV DNA suppression < 400 copies/ml.

Experience beyond 48 weeks in studies GS-US-174-0102 and GS-US-174-0103: In studies GS-US-174-0102 and GS-US-174-0103, after receiving double-blind treatment for 48 weeks (either tenofovir disoproxil 245 mg (as fumarate) or adefovir dipivoxil 10 mg), patients rolled over with no interruption in treatment to open-label tenofovir disoproxil fumarate. In studies GS-US-174-0102 and GS-US-174-0103, 84% and 74% of patients continued treatment through 192 weeks, respectively. At weeks 96, 144,192 and 240, viral suppression, biochemical and serological responses were maintained with continued tenofovir disoproxil fumarate treatment (see Table 4 below).

Table 4: Efficacy parameters in compensated HBeAg positive and HBeAg negative patients at week 96, 144,192 and 240 open-label treatment

	Study 174-0102 (HBeAg negative)								Study 174-0103 (HBeAg positive)							
Parametera	**Tenofovir disoproxil 245 mg (as fumarate) n = 250**				**Adefovir dipivoxil 10 mg roll over to tenofovir disoproxil 245 mg (as fumarate) n = 125**				**Tenofovir disoproxil 245 mg (as fumarate) n = 176**				**10 mg roll over to tenofovir disoproxil 245 mg (as fumarate) n = 90**			
Week	96 b	144 e	192 h	240 j	96 c	144 f	192 i	240 k	96 b	144 e	192 h	240 j	96 c	144 f	192 i	240 k
HBV DNA (%) <400copies/ml (<69IU/ml)	90	87	84	83	89	88	87	84	76	72	68	64	74	71	72	66
ALT (%) Normalised ALTd	72	73	67	70	68	70	77	76	60	55	56	46	65	61	59	56
Serology (%) HBeAg loss/ seroconversion	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	26/ 23	29/ 23	34/ 25	38/ 30	24/ 20	33/ 26	36/ 30	38/ 31
HBsAg loss/ seroconversion	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0[l]	5/4	8/ 6[g]	11/ 8[g]	11/ 8[m]	6/5	8/ 7[g]	8/ 7[g]	1 10/ 10[m]

[a] Based upon Long Term Evaluation algorithm (LTE Analysis) - Patients who discontinued the study at any time prior to week 240 due to a protocol defined endpoint, as well as those completing week 240, are included in the denominator.

[b] 48 weeks double-blind tenofovir disoproxil fumarate followed by 48 weeks open-label.

[c] 48 weeks double-blind adefovir dipivoxil followed by 48 weeks open-label tenofovir disoproxil fumarate.

[d] The population used for analysis of ALT normalisation included only patients with ALT above ULN at baseline.

[e] 48 weeks double-blind tenofovir disoproxil fumarate followed by 96 weeks open-label.

[f] 48 weeks double-blind adefovir dipivoxil followed by 96 weeks open-label tenofovir disoproxil fumarate.

[g] Figures presented are cumulative percentages based upon a Kaplan Meier analysis including data collected after the addition of emtricitabine to open-label tenofovir disoproxil fumarate (KM-ITT).

[h] 48 weeks double-blind tenofovir disoproxil fumarate followed by 144 weeks open-label.

[i] 48 weeks double-blind adefovir dipivoxil followed by 144 weeks open-label tenofovir disoproxil fumarate.

[j] 48 weeks double-blind tenofovir disoproxil fumarate followed by 192 weeks open-label.

[k] 48 weeks double-blind adefovir dipivoxil followed by 192 weeks open-label tenofovir disoproxil fumarate.

[l] One patient in this group became HBsAg negative for the first time at the 240 week visit and was ongoing in the study at the time of the data cut-off. However, the subject's HBsAg loss was ultimately confirmed at the subsequent visit.

[m] Figures presented are cumulative percentages based upon a Kaplan Meier analysis excluding data collected after the addition of emtricitabine to open-label tenofovir disoproxil fumarate (KM-TDF).

n/a = not applicable.

Paired baseline and week 240 liver biopsy data were available for 331/489 patients who remained in studies GS-US-174-0102 and GS-US-174-0103 (seed Table 5 below). Ninety-five percent (225/237) of patients without cirrhosis at baseline and 99% (93/94) of patients with cirrhosis at baseline had either no change or an improvement in fibrosis (Ishak fibrosis score). Of the 94 patients with cirrhosis at baseline (Ishak fibrosis score 5-6), 26% (24) experienced no change in Ishak fibrosis score and 72% (68) experienced regression of cirrhosis by week 240 with a reduction in Ishak fibrosis score of at least 2 points.

Table 5: Histological response (%) in compensated HBeAg negative and HBeAg positive subjects at week 240 compared to baseline

	Study 174-0102 (HBeAg negative)		Study 174-0103 (HBeAg positive)	
Parameter	Tenofovir disoproxil 245 mg (as fumarate) n = 250[c]	10 mg roll over to tenofovir disoproxil 245 mg (as fumarate) n = 125[d]	Tenofovir disoproxil 245 mg (as fumarate) n = 176[c]	Adefovir dipivoxil 10 mg roll over to tenofovir disoproxil 245 mg (as fumarate) n = 90[d]
Histological response[a,b] (%)	88 [130/148]	85 [63/74]	90 [63/70]	92 [36/39]

[a] The population used for analysis of histology included only patients with available liver biopsy data (Missing = Excluded) by week 240. Response after addition of emtricitabine is excluded (total of 17 subjects across both studies).

[b] Knodell necroinflammatory score improvement of at least 2 points without worsening in Knodell fibrosis score.

[c] 48 weeks double-blind tenofovir disoproxil fumarate followed by up to 192 weeks open-label.

[d] 48 weeks double-blind adefovir dipivoxil followed by up to 192 weeks open-label tenofovir disoproxil fumarate.

Experience in patients with HIV co-infection and prior lamivudine experience: In a randomised, 48-week double-blind, controlled study of tenofovir disoproxil 245 mg (as fumarate) in patients co-infected with HIV-1 and chronic hepatitis B with prior lamivudine experience (study ACTG 5127), the mean serum HBV DNA levels at baseline in patients randomised to the tenofovir arm were 9.45 log_{10} copies/ml (n = 27). Treatment with tenofovir disoproxil 245 mg (as fumarate) was associated with a mean change in serum HBV DNA from baseline, in the patients for whom there was 48-week data, of -5.74 log_{10} copies/ml (n = 18). In addition, 61% of patients had normal ALT at week 48.

Experience in patients with persistent viral replication: The efficacy and safety of tenofovir disoproxil 245 mg (as fumarate) or tenofovir disoproxil 245 mg (as fumarate) plus 200 mg emtricitabine has been evaluated in a randomised, double-blind study (study GS-US-174-0106), in HBeAg positive and HBeAg negative patients who had persistent viraemia (HBV DNA 1,000 copies/ml) while receiving adefovir dipivoxil 10 mg for more than 24 weeks. At baseline, 57% of patients randomised to tenofovir disoproxil fumarate versus 60% of patients randomised to emtricitabine plus tenofovir disoproxil fumarate treatment group had previously been treated with lamivudine. Overall at week 24, treatment with tenofovir disoproxil fumarate resulted in 66% (35/53) of patients with HBV DNA < 400 copies/ml (< 69 IU/ml) versus 69% (36/52) of patients treated with emtricitabine plus tenofovir disoproxil fumarate (p = 0.672). In addition 55% (29/53) of patients treated with tenofovir disoproxil fumarate had undetectable HBV DNA (< 169 copies/ml [< 29 IU/ml]; the limit of quantification of the Roche Cobas TaqMan HBV assay) versus 60% (31/52) of patients treated with emtricitabine plus tenofovir disoproxil fumarate (p = 0.504). Comparisons between treatment groups beyond week 24 are difficult to interpret since investigators had the option to intensify treatment to open-label emtricitabine plus tenofovir disoproxil. Long-term studies to evaluate the benefit/risk of bitherapy with emtricitabine plus tenofovir disoproxil fumarate in HBV monoinfected patients are ongoing.

Experience in patients with decompensated liver disease at 48 weeks: Study GS-US-174-0108 is a randomised, double-blind, active controlled study evaluating the safety and efficacy of tenofovir disoproxil fumarate (n = 45), emtricitabine plus tenofovir disoproxil fumarate (n = 45), and entecavir (n = 22), in patients with decompensated liver disease. In the tenofovir disoproxil fumarate treatment arm, patients had a mean CPT score of 7.2, mean HBV DNA of 5.8 log_{10} copies/ml and mean serum ALT of 61 U/l at baseline. Forty-two percent (19/45) of patients had at least 6 months of prior lamivudine experience, 20% (9/45) of patients had prior adefovir dipivoxil experience and 9 of 45 patients (20%) had lamivudine and/or adefovir dipivoxil resistance mutations at baseline. The co-primary safety endpoints were discontinuation due to an adverse event and confirmed increase in serum creatinine 0.5 mg/dl or confirmed serum phosphate of < 2 mg/dl.

In patients with CPT scores 9, 74% (29/39) of tenofovir disoproxil fumarate, and 94% (33/35) of emtricitabine plus tenofovir disoproxil fumarate treatment groups achieved HBV DNA < 400 copies/ml after 48 weeks of treatment.

Overall, the data derived from this study are too limited to draw any definitive conclusions on the comparison of emtricitabine plus tenofovir disoproxil fumarate versus tenofovir disoproxil fumarate, (see Table 6 below).

Table 6: Safety and efficacy parameters in decompensated patients at week 48

	Study 174-0108		
Parameter	**Tenofovir disoproxil 245 mg (as fumarate) (n = 45)**	**Emtricitabine 200 mg/ tenofovir disoproxil 245 mg (as fumarate) (n = 45)**	**Entecavir (0.5 mg or 1 mg) n = 22**
Tolerability failure n (%)[a]	3 (7%)	2 (4%)	2 (9%)
Confirmed increase in serum creatinine ≥ 0.5 mg/dl from baseline or confirmed serum phosphate of < 2 mg/dl n (%)[b]	4 (9%)	3 (7%)	1 (5%)
HBV DNA n (%) < 400 copies/ml n (%)	31/44 (70%)	36/41 (88%)	16/22 (73%)
ALT n (%) Normal ALT	25/44 (57%)	31/41 (76%)	12/22 (55%)
≥ 2 point decrease in CPT from baseline n (%)	7/27 (26%)	12/25 (48%)	5/12 (42%)
Mean change from baseline in CPT score	-0.8	-0.9	-1.3
Mean change from baseline in MELD score	-1.8	-2.3	-2.6

[a] p-value comparing the combined tenofovir-containing arms versus the entecavir arm = 0.622,

[b] p-value comparing the combined tenofovir-containing arms versus the entecavir arm = 1.000.

Clinical resistance: Four hundred and twenty-six HBeAg negative (GS-US-174-0102, n = 250) and HBeAg positive (GS-US-174-0103, n = 176) patients were evaluated for genotypic changes in HBV polymerase from baseline. Genotypic evaluations performed on all patients initially randomised to the tenofovir disoproxil fumarate arm (i.e. excluding patients who received double-blind adefovir dipivoxil and then switched to open-label tenofovir disoproxil fumarate) with HBV DNA > 400 copies/ml at week 48 (n = 39), week 96 (n = 24), week 144 (n = 6), week 192 (n = 5) and week 240 (n = 4) on tenofovir disoproxil fumarate monotherapy, showed that no mutations associated with tenofovir disoproxil fumarate resistance have developed.

In study GS-US-174-0108, 45 patients (including 9 patients with lamivudine and/or adefovir dipivoxil resistance mutations at baseline) received tenofovir disoproxil fumarate for up to 48 weeks. Genotypic data from paired baseline and on treatment HBV isolates were available for 6/8 patients with HBV DNA > 400 copies/ml. No amino acid substitutions associated with resistance to tenofovir disoproxil fumarate were identified in these isolates.

Paediatric population: In study GS-US-104-0321, 87 HIV-1 infected treatment-experienced patients 12 to < 18 years of age were treated with tenofovir disoproxil fumarate (n = 45) or placebo (n = 42) in combination with an optimised background regimen (OBR) for 48 weeks. The mean baseline CD4 cell count was 374 cells/mm³ and the mean baseline plasma HIV-1 RNA was 4.6 log_{10} copies/ml. The primary efficacy endpoint was time-weighted average change from baseline through week 24 (DAVG24) in plasma HIV-1 RNA. No additional benefit over OBR was observed with the addition of tenofovir disoproxil fumarate compared to placebo (DAVG24 -1.58 log_{10} copies/ml versus -1.55 log_{10} copies/ml respectively, p = 0.55). K65R developed in 1 subject in the tenofovir disoproxil fumarate group.

In patients who received treatment with tenofovir disoproxil fumarate or placebo, mean lumbar spine BMD Z-score was -1.004 and -0.809, and mean total body BMD Z-score was -0.866 and -0.584, respectively, at baseline. Mean changes at week 48 (end of double-blind phase) were -0.215 and -0.165 in lumbar spine BMD Z-score, and -0.254 and -0.179 in total body BMD Z-score for the tenofovir disoproxil fumarate and placebo groups, respectively. The mean rate of BMD gain was less in the tenofovir disoproxil fumarate group compared to the placebo group. At week 48, six adolescents in the tenofovir disoproxil fumarate group and one adolescent in the placebo group had significant lumbar spine BMD loss (defined as > 4% loss). Among 28 patients receiving 96 weeks of treatment with tenofovir disoproxil fumarate, BMD Z-scores declined by -0.341 for lumbar spine and -0.458 for total body.

The efficacy and safety data derived from this study do not support the use of Tenofovir Disoproxil Fumarate Tablet in adolescents.

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. Administration of multiple doses of tenofovir disoproxil fumarate with a meal to HIV infected patients resulted in mean (%CV) tenofovir C_{max}, $AUC_{0-\infty}$ and C_{min} values of 326 (36.6%) ng/ml, 3,324 (41.2%) ng•hr/ml and 64.4 (39.4%) ng/ml, respectively. Maximum tenofovir concentrations are observed in serum within one hour of dosing in the fasted state and within two hours when taken with food. The oral bioavailability of tenofovir from tenofovir disoproxil fumarate in fasted patients was approximately 25%. Administration of tenofovir disoproxil fumarate with a high fat meal enhanced the oral bioavailability, with an increase in tenofovir AUC by approximately 40% and C_{max} by approximately 14%. Following the first dose of tenofovir disoproxil fumarate in fed patients, the median C_{max} in serum ranged from 213 to 375 ng/ml. However, 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. After oral administration of tenofovir disoproxil fumarate, tenofovir is distributed to most tissues with the highest concentrations occurring in the kidney, liver and the intestinal contents (preclinical studies). *In vitro* protein binding of tenofovir to plasma or serum protein was less than 0.7 and 7.2%, respectively, over the tenofovir concentration range 0.01 to 25 µg/ml.

Biotransformation

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

Elimination

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

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).

Linearity/non-linearity

The pharmacokinetics of tenofovir were independent of tenofovir disoproxil fumarate dose over the dose range 75 to 600 mg and were not affected by repeated dosing at any dose level.

Age: Pharmacokinetic studies have not been performed in the elderly (over 65 years of age).

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

Ethnicity: Pharmacokinetics have not been specifically studied in different ethnic groups.

Paediatric population: Steady-state pharmacokinetics of tenofovir were evaluated in 8 HIV-1 infected adolescent patients (aged 12 to < 18 years) with body weight 35 kg. Mean (± SD) C_{max} and AUC_{tau} are 0.38 ± 0.13 µg/ml and 3.39 ± 1.22 µg•h/ml, respectively. Tenofovir exposure achieved in adolescent patients receiving oral daily doses of tenofovir disoproxil 245 mg (as fumarate) was similar to exposures achieved in adults receiving once-daily doses of tenofovir disoproxil 245 mg (as fumarate).

Pharmacokinetic studies have not been performed in children under 12 years or with renal impairment.

Renal impairment

Pharmacokinetic parameters of tenofovir were determined following administration of a single dose of tenofovir disoproxil 245 mg to 40 non-HIV infected patients with varying degrees of renal impairment defined according to baseline creatinine clearance (CrCl) (normal renal function when CrCl> 80 ml/min; mild with CrCl = 50-79 ml/min; moderate with CrCl = 30-49 ml/min and severe with CrCl = 10-29 ml/min). Compared with patients with normal renal function, the mean (%CV) tenofovir exposure increased from 2,185 (12%) ng•h/ml in subjects with CrCl> 80 ml/min to respectively 3,064 (30%) ng•h/ml, 6,009 (42%) ng•h/ml and 15,985 (45%) ng•h/ml in patients with mild, moderate and severe renal impairment. The dosing recommendations in patients with renal impairment, with increased dosing interval, are expected to result in higher peak plasma concentrations and lower C_{min} levels in patients with renal impairment compared with patients with normal renal function. The clinical implications of this are unknown.

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

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

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

Hepatic Impairment

A single 245 mg dose of tenofovir disoproxil was administered to non-HIV infected patients with varying degrees of hepatic impairment defined according to Child-Pugh-Turcotte (CPT) classification. Tenofovir pharmacokinetics were not substantially altered in subjects with hepatic impairment suggesting that no dose adjustment is required in these subjects. The mean (%CV) tenofovir C_{max} and $AUC_{0-\infty}$ values were 223 (34.8%) ng/ml and 2,050 (50.8%) ng•hr/ml, respectively, in normal subjects compared with 289 (46.0%) ng/ml and 2,310 (43.5%) ng•hr/ml in subjects with moderate hepatic impairment, and 305 (24.8%) ng/ml and 2,740 (44.0%) ng•hr/ml in subjects with severe hepatic impairment.

Intracellular pharmacokinetics

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

Preclinical safety data

Non-clinical safety pharmacology studies reveal no special hazard for humans. Findings in repeated dose toxicity studies in rats, dogs and monkeys at exposure levels greater than or equal to clinical exposure levels and with possible relevance to clinical use include renal and bone toxicity and a decrease in serum phosphate concentration. Bone toxicity was diagnosed as osteomalacia (monkeys) and reduced bone mineral density (BMD) (rats and dogs). The bone toxicity in young adult rats and dogs occurred at exposures 5-fold the exposure in paediatric or adult patients; bone toxicity occurred in juvenile infected monkeys at very high exposures following subcutaneous dosing (40-fold the exposure in patients). 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 BMD.

Genotoxicity studies revealed positive results in the in vitro mouse lymphoma assay, equivocal results in one of the strains used in the Ames test, and weakly positive results in an UDS test in primary rat hepatocytes. However, it was negative in an in vivo mouse bone marrow micronucleus assay.

Oral carcinogenicity studies in rats and mice only revealed a low incidence of duodenal tumours at an extremely high dose in mice. These tumours are unlikely to be of relevance to humans.

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.

Special precautions for storage

Store protected from moisture & light, at a temperature not exceeding 30°C.

Keep the container tightly closed.

Pack

HDPE bottle of 30's.

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