

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Viread 245 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient(s):

Each tablet contains 153.33 mg lactose monohydrate. For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Light blue, almond-shaped, film-coated tablets, debossed on one side with the markings “GILEAD” and “4331” and on the other side with the marking “300”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

HIV-1 infection

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

The demonstration of benefit of Viread 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 Viread 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 Viread to treat antiretroviral experienced patients with HIV-1 infection should be based on individual viral resistance testing and/or treatment history of patients.

Hepatitis B infection

Viread is indicated for the treatment of chronic hepatitis B (see section 5.1) 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 (see sections 4.4, 4.8 and 5.1).

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.

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

Adults: The recommended dose for the treatment of HIV or for the treatment of chronic hepatitis B is 245 mg (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 (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 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.

Paediatric patients: Viread is not recommended for use in children below the age of 18 years due to insufficient data on safety and efficacy (see section 5.2).

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 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. Dose interval adjustments are recommended for 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 245 mg 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 (see sections 4.4 and 5.2).

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: 245 mg tenofovir disoproxil (as fumarate) may be administered every 72-96 hours (dosing twice a week).

Haemodialysis patients: 245 mg 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 (see sections 4.4 and 5.2).

* 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 (see sections 4.4 and 5.2).

If Viread 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 (see section 4.4).

4.3 Contraindications

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

4.4 Special warnings and precautions for use

General: Tenofovir disoproxil fumarate has not been studied in patients under the age of 18 or 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 (see below).

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.

Viread 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:

- Viread should not be administered with any other medicinal products containing tenofovir disoproxil fumarate (Truvada or Atripla).
- Viread should also not be administered concurrently 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 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 co-administered with tenofovir disoproxil fumarate therapy has been associated with reports of high rates of virological failure within several tested combinations for the treatment of HIV-1 infection.

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

Renal function: 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 (see section 4.8).

Renal safety with tenofovir has only been studied to a very limited degree in patients with impaired renal function (CrCl < 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) 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 (see sections 4.2 and 5.2).

If serum phosphate is < 1.5 mg/dl (0.48 mmol/l) or creatinine clearance is decreased to < 50 ml/min in any patient receiving tenofovir disoproxil fumarate, 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 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. cidofovir, a known nephrotoxic medicinal product). These renal transport proteins may be responsible for tubular secretion and in part, renal elimination of tenofovir 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 4 might be modified if they are co-administered. Unless clearly necessary, concomitant use of these medicinal products which are secreted by the same renal pathway is not recommended, but if such use is unavoidable, renal function should be monitored weekly (see section 4.5).

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 bone mineral density of spine and changes in bone biomarkers from baseline were significantly greater in the tenofovir disoproxil fumarate treatment group 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.

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 (see section 4.8). 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 hyperlactataemia) 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 hyperlactataemia 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 (lipoatrophy/lipomatosis): In HIV infected patients, combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy). 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 (see section 4.8).

Tenofovir is structurally related to nucleoside analogues hence the risk of lipodystrophy cannot be excluded. However, 144-week clinical data from antiretroviral-naïve HIV infected 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 national 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.

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:

Viread should not be administered with any other medicinal products containing tenofovir disoproxil fumarate (Truvada or Atripla).

Viread 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 1).

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 (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 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 (see section 4.4).
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% C _{max} : ↔ C _{min} : ↑ 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 (300/100 b.i.d./300 q.d.)	Darunavir: No significant effect on darunavir/ritonavir PK parameters. Tenofovir: AUC: ↑ 22% C _{min} : ↑ 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	Co-administration of tenofovir disoproxil fumarate and didanosine results in a 40-60% increase in systemic exposure to didanosine that may increase the risk for didanosine-related adverse events. Rare cases of pancreatitis and lactic acidosis, sometimes fatal, have been reported. 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 (see section 4.4).
Adefovir dipivoxil	AUC: ↔ C _{max} : ↔	Tenofovir disoproxil fumarate should not be administered concurrently with adefovir dipivoxil (see section 4.4).
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 (see section 5.2).

4.6 Pregnancy and lactation

Pregnancy

For tenofovir disoproxil fumarate limited clinical data on exposed pregnancies are available.

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).

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

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

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. Therefore, it is recommended that mothers being treated with tenofovir disoproxil fumarate do not breast-feed their infants.

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

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

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 Viread (see section 4.4).

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 (see sections 4.4 and 4.8c).

Co-administration of Viread and didanosine is not recommended as this may result in an increased risk of adverse reactions (see section 4.5). Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported (see section 4.4).

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 (see section 4.4).

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 from HIV-1 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 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.

Continued treatment with tenofovir disoproxil fumarate for up to 144 weeks in these studies did not reveal any new adverse reactions and no change in the tolerability profile (nature or severity of adverse events).

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 (see section 4.4).

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 frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), or rare ($\geq 1/10,000$ to $< 1/1,000$).

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

Frequency	Tenofovir disoproxil fumarate
<i>Metabolism and nutrition disorders:</i>	
Very common:	hypophosphataemia ¹
Uncommon:	hypokalaemia ¹
Rare:	lactic acidosis ³
<i>Nervous system disorders:</i>	
Very common:	dizziness
Common:	headache
<i>Gastrointestinal disorders:</i>	
Very common:	diarrhoea, vomiting, nausea
Common:	abdominal pain, abdominal distension, flatulence
Uncommon:	pancreatitis ³
<i>Hepatobiliary disorders:</i>	
Common:	increased transaminases
Rare:	hepatic steatosis ³ , hepatitis
<i>Skin and subcutaneous disorders:</i>	
Very common:	rash
Rare:	angioedema
<i>Musculoskeletal and connective tissue disorders:</i>	
Uncommon:	rhabdomyolysis ¹ , muscular weakness ¹
Rare:	osteomalacia (manifested as bone pain and infrequently contributing to fractures) ^{1, 2} , myopathy ¹
<i>Renal and urinary disorders:</i>	
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

<i>General disorders and administration site conditions:</i>	
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:

As Viread may cause renal damage monitoring of renal function is recommended (see sections 4.4 and 4.8a).

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 events (see section 4.5). Rare cases of 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 (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 intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump) (see section 4.4).

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

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 (see section 4.4).

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 (see section 4.4).

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 (see section 4.4).

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 $\geq 2 \log_{10}$ copies/ml reduction in viral load that preceded or coincided with the ALT elevation. Periodic monitoring of hepatic function is recommended during treatment (see section 4.4).

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 (see section 4.4).

d. Paediatric population

Insufficient safety data are available for children below 18 years of age. Viread is not recommended in this population (see section 4.2).

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 (see section 4.4).

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 Viread (see sections 4.2, 4.4 and 5.2).

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 has an intracellular half-life of 10 hours in activated and 50 hours in resting peripheral blood mononuclear cells (PBMCs). 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 $\mu\text{mol/l}$, 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-1_{IIIB} is 1-6 $\mu\text{mol/l}$ in lymphoid cell lines and 1.1 $\mu\text{mol/l}$ 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 $\mu\text{mol/l}$ 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 (see section 4.4).

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 results: The effects of tenofovir disoproxil fumarate in treatment-experienced and treatment-naïve HIV-1 infected adults have been demonstrated in trials of 48 weeks duration in treatment-experienced HIV-1 infected adults.

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 log₁₀ 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 log₁₀ copies/ml and -0.61 log₁₀ 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 log₁₀ 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 log₁₀ 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 log₁₀ 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 log₁₀ 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 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 (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 EC₅₀ values 1.5-fold that of wild-type virus.

Clinical results: 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

Parameter	Study 174-0102 (HBeAg negative)		Study 174-0103 (HBeAg positive)	
	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 study GS-US-174-0102, 90% and 88% of patients and in study GS-US-174-0103, 82% and 92% of patients who were randomised to tenofovir disoproxil fumarate or adefovir dipivoxil, respectively, completed 96 weeks of treatment. In study GS-US-174-0102, 328 of 375 patients (87%) continued treatment through week 144, while in study GS-US-174-0103, 214 of 266 patients (80%) continued treatment through week 144. At both week 96 and week 144, 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 and week 144 open-label treatment

Parameter ^a	Study 174-0102 (HBeAg negative)				Study 174-0103 (HBeAg positive)			
	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		Adefovir dipivoxil 10 mg roll over to tenofovir disoproxil 245 mg (as fumarate) n = 90	
	96 weeks ^b	144 weeks ^c	96 weeks ^c	144 weeks ^f	96 weeks ^b	144 weeks ^e	96 weeks ^c	144 weeks ^f
HBV DNA (%) < 400 copies/ml (< 69 IU/ml)	90	87	89	88	76	72	74	71
ALT (%) Normalised ALT ^d	72	73	68	70	60	55	65	61
Serology (%)	N/A	N/A	N/A	N/A	26/23	29/23	24/20	33/26
HBeAg loss/seroconversion								
HBsAg loss/seroconversion	0/0	0/0	0/0	0/0	5/4	8/6 ^g	6/5	8/7 ^g

^a Based upon Long Term Evaluation algorithm (LTE Analysis) - Patients who discontinued the study at any time prior to week 144 due to a protocol defined endpoint, as well as those completing week 144, 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 (KM-ITT), N/A= not applicable.

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 log₁₀ 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 log₁₀ 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 5 below).

Table 5: Safety and efficacy parameters in decompensated patients at week 48

Parameter	Study 174-0108		
	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) and week 144 (n = 6) 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.

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. 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·h/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 and gender

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

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

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

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

It is recommended that the dosing interval for tenofovir disoproxil 245 mg (as fumarate) 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 245 mg dose of tenofovir disoproxil was administered to non-HIV, non-HBV 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-∞} values were 223 (34.8%) ng/ml and 2,050 (50.8%) ng·h/ml, respectively, in normal subjects compared with 289 (46.0%) ng/ml and 2,310 (43.5%) ng·h/ml in subjects with moderate hepatic impairment, and 305 (24.8%) ng/ml and 2,740 (44.0%) ng·h/ml in subjects with severe hepatic impairment.

Intracellular pharmacokinetics

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

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

Core:

Microcrystalline cellulose (E460)
Pregelatinised starch (gluten free)
Croscarmellose sodium
Lactose monohydrate
Magnesium stearate (E572)

Coating:

Lactose monohydrate
Hypromellose (E464)
Titanium dioxide (E171)
Glycerol triacetate (E1518)
Indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Viread is supplied in high density polyethylene (HDPE) bottles with a child-resistant closure containing 30 film-coated tablets with a silica gel desiccant.

The following pack sizes are available: outer cartons containing 1 x 30 film-coated tablet and 3 x 30 film-coated tablet bottles. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Gilead Sciences International Limited
Cambridge
CB21 6GT
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/200/001
EU/1/01/200/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 5 February 2002
Date of last renewal: 7 February 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) <http://www.ema.europa.eu/>.

ANNEX II

- A. MANUFACTURING AUTHORISATION HOLDER(S)
RESPONSIBLE FOR BATCH RELEASE**

- B. CONDITIONS OF THE MARKETING AUTHORISATION**

A. MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

Names and addresses of the manufacturers responsible for batch release

Nycomed Oranienburg GmbH
Lehnitzstrasse 70-98
D-16515 Oranienburg
Germany

Gilead Sciences Limited
Unit 13, Stillorgan Industrial Park
Blackrock Co. Dublin
Ireland

Gilead Sciences Limited
IDA Business & Technology Park
Carrigtohill Co. Cork
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OF THE MARKETING AUTHORISATION

• CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

• CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Not applicable.

• OTHER CONDITIONS

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, as described in version 6.0 (13/05/2010) and included in the Type IA variation EMEA/H/C/419/IA/099 and subsequent updates, is in place and functioning before and whilst the product is on the market.

Risk Management Plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 8.1 of the Risk Management Plan (RMP) presented in Module 1.8.2 of the Marketing Authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency

PSURs:

The Marketing Authorisation Holder will submit PSUR's on an annual basis.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON AND BOTTLE LABEL TEXT

1. NAME OF THE MEDICINAL PRODUCT

Viread 245 mg film-coated tablets
Tenofovir disoproxil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 245 mg tenofovir disoproxil equivalent to 300 mg tenofovir disoproxil fumarate.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate, see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets.
3 x 30 film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gilead Sciences Intl Ltd
Cambridge
CB21 6GT
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/200/001 30 film-coated tablets
EU/1/01/200/002 3 x 30 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Viread [outer packaging only]

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Viread 245 mg film-coated tablets Tenofovir disoproxil

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Viread is and what it is used for
2. Before you take Viread
3. How to take Viread
4. Possible side effects
5. How to store Viread
6. Further information

1. WHAT VIREAD IS AND WHAT IT IS USED FOR

Viread is a treatment for Human Immunodeficiency Virus (HIV) infection in adults over 18 years of age.

Viread is also used to treat chronic hepatitis B, an infection with hepatitis B virus (HBV), in adults.

You do not have to have HIV to be treated with Viread for HBV.

Viread contains the active substance, *tenofovir disoproxil*. This active substance is an *antiretroviral* or antiviral medicine which is used to treat HIV or HBV or both. Tenofovir is a *nucleotide reverse transcriptase inhibitor*, generally known as an NRTI and works by interfering with the normal working of enzymes (in HIV *reverse transcriptase*; in hepatitis B *DNA polymerase*) that are essential for the viruses to reproduce themselves. In HIV Viread should always be used combined with other medicines to treat HIV infection.

This medicine is not a cure for HIV infection. While taking Viread you may still develop infections or other illnesses associated with HIV infection.

You can also pass on HIV or HBV to others, so it is important to take precautions to avoid infecting other people.

2. BEFORE YOU TAKE VIREAD

Do not take Viread

- **If you are allergic** (hypersensitive) to tenofovir, tenofovir disoproxil fumarate or any of the other ingredients of Viread listed at the end of this leaflet.

If this applies to you, tell your doctor immediately and don't take Viread.

Take special care with Viread

- **Tell your doctor if you have had kidney disease or if tests have shown problems with your kidneys.** Viread may affect your kidneys. Before starting treatment, your doctor may order blood tests to check your kidney function and may advise you to take the tablets less often. Your doctor may also order blood tests during treatment to monitor your kidneys.

Viread is not usually taken with other medicines that can damage your kidneys (see *Taking other medicines*). If this is unavoidable, your doctor will monitor your kidney function once a week.

- **Talk to your doctor if you are over 65.** Viread has not been studied in patients over 65 years of age. If you are older than this and are prescribed Viread, your doctor will monitor you carefully.
- **Do not give Viread to children and adolescents** under 18 years of age.
- **Talk to your doctor if you have a history of liver disease, including hepatitis.** Patients with liver disease including chronic hepatitis B or C, who are treated with antiretrovirals, have a higher risk of severe and potentially fatal liver complications. If you have hepatitis B infection, your doctor will carefully consider the best treatment for you. If you have a history of liver disease or chronic hepatitis B infection your doctor may conduct blood tests to monitor your liver function.

Look out for possible signs of lactic acidosis (excess of lactic acid in your blood) once you start taking Viread. Possible signs of lactic acidosis are:

- Deep, rapid breathing
 - drowsiness
 - nausea, vomiting and stomach pain
- This rare but serious side effect can cause enlargement of the liver and has occasionally been fatal. Lactic acidosis occurs more often in women, particularly if they are very overweight. If you have liver disease you may also be more at risk of getting this condition. While you are being treated with Viread, your doctor will monitor you closely for any signs that you may be developing lactic acidosis.
 - **Take care not to infect other people.** Viread does not reduce the risk of passing on HIV or HBV to others through sexual contact or blood contamination. You must continue to take precautions to avoid this.

Other precautions

In the treatment of HIV, combination antiretroviral therapies (including Viread) may raise blood sugar, increase blood fats (hyperlipaemia), cause changes to body fat, and resistance to insulin (see section 4, *Possible side effects*).

If you are diabetic, overweight or have high cholesterol, talk to your doctor.

Look out for infections. If you have advanced HIV infection (AIDS) and have an infection, you may develop symptoms of infection and inflammation or worsening of the symptoms of an existing infection once treatment with Viread is started. These symptoms may indicate that your body's improved immune system is fighting infection. Look out for signs of inflammation or infection soon after you start taking Viread. If you notice signs of inflammation or infection, **tell your doctor at once.**

Bone problems. Some patients with HIV taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms tell your doctor.

Bone problems (sometimes resulting in fractures) may also occur due to damage to kidney tubule cells (see section 4, *Possible side effects*).

Taking other medicines

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

- **Don't stop any anti-HIV medicines** prescribed by your doctor when you start Viread if you have both HBV and HIV.
- **Do not take Viread** if you are already taking other medicines containing tenofovir disoproxil fumarate. Do not take Viread and Hepsara (adefovir dipivoxil) at the same time.
- **It is very important to tell your doctor if you are taking other medicines that may damage your kidneys.**

These include:

- aminoglycosides, pentamidine or vancomycin (for bacterial infection)
 - amphotericin B (for fungal infection)
 - foscarnet, ganciclovir, or cidofovir (for viral infection)
 - interleukin-2 (to treat cancer)
 - adefovir dipivoxil (for HBV)
 - tacrolimus (for suppression of the immune system)
- **Other medicines containing didanosine (for HIV infection):** Taking Viread with other antiviral medicines that contain didanosine can raise the levels of didanosine in your blood and may reduce CD4 cell counts. Rarely, inflammation of the pancreas and lactic acidosis (excess lactic acid in the blood), which sometimes caused death, have been reported when medicines containing tenofovir disoproxil fumarate and didanosine were taken together. Your doctor will carefully consider whether to treat you with combinations of tenofovir and didanosine.

Taking Viread with food and drink

- **Take Viread with food** (for example, a meal or a snack).

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

- **You must not take Viread during pregnancy** unless specifically discussed with your doctor. There are no clinical data on the use of Viread in pregnant women and it is not usually used unless absolutely necessary.
- **Try to avoid getting pregnant** during treatment with Viread. You must use an effective method of contraception to avoid becoming pregnant.

- **If you become pregnant**, or plan to become pregnant, ask your doctor about the potential benefits and risks of your antiretroviral therapy to you and your child.
- **If you have taken Viread** during your pregnancy, your doctor may request regular blood tests and other diagnostic tests to monitor the development of your child. In children whose mothers took medicines like Viread (NRTIs) during pregnancy, the benefit from the protection against the virus outweighed the risk of side effects.
- **Do not breast-feed during treatment with Viread.** It is not yet known whether the active substance in this medicine passes into human breast milk.
- If you are a woman with HIV or HBV do not breast-feed, to avoid passing the virus to the baby in breast milk.

Driving and using machines

Viread can cause dizziness. If you feel dizzy while taking Viread, **do not drive** and do not use any tools or machines.

Important information about some of the ingredients of Viread

Viread contains lactose. **Tell your doctor before taking Viread** if you cannot tolerate lactose or if you have an intolerance to any other sugars.

3. HOW TO TAKE VIREAD

- **Always take Viread exactly as your doctor has told you.** You should check with your doctor or pharmacist if you are not sure.

The usual dose:

- **Adults: one tablet each day with food** (for example, a meal or a snack).
- **Not for children and adolescents** (under 18 years of age).

If you have particular difficulty swallowing, you can use the tip of a spoon to crush the tablet. Then mix the powder with about 100 ml (half a glass) of water, orange juice or grape juice and drink immediately.

- **Always take the dose recommended by your doctor.** This is to make sure that your medicine is fully effective, and to reduce the risk of developing resistance to the treatment. Do not change the dose unless your doctor tells you to.
- **If you have problems with your kidneys**, your doctor may advise you to take Viread less frequently.
- **Don't stop any anti-HIV medicines** prescribed by your doctor when you start Viread if you have both HBV and HIV.
- If you have HBV your doctor may offer you an HIV test to see if you have both HBV and HIV.

Please refer to the patient information leaflets of the other antiretrovirals for guidance on how to take those medicines.

If you take more Viread than you should

If you accidentally take too many Viread tablets, contact your doctor or nearest emergency department for advice. Keep the tablet bottle with you so that you can easily describe what you have taken.

If you forget to take Viread

It is important not to miss a dose of Viread.

If you miss a dose of Viread, take it as soon as you can, and then take your next dose at its regular time.

If it is almost time for your next dose anyway, forget about the missed dose. Wait and take the next dose at the regular time. Do not take a double dose to make up for a forgotten tablet.

If you throw up less than 1 hour after taking Viread, take another tablet. You do not need to take another tablet if you were sick more than 1 hour after taking Viread.

If you stop taking Viread

- Don't stop taking Viread without your doctor's advice. Stopping treatment with Viread may reduce the effectiveness of the treatment recommended by your doctor. Talk to your doctor before you stop taking Viread for any reason, particularly if you are experiencing any side effects or you have another illness. Contact your doctor before you restart taking Viread tablets.
- **If you have hepatitis B or HIV and hepatitis B together (co-infection)**, it is very important not to stop your Viread treatment without talking to your doctor first. Some patients have had blood tests or symptoms indicating that their hepatitis has got worse after stopping Viread. You may require blood tests for several months after stopping treatment. In some patients with advanced liver disease or cirrhosis, stopping treatment is not recommended as this may lead to worsening of your hepatitis.

Tell your doctor immediately about new or unusual symptoms after you stop treatment, particularly symptoms you associate with hepatitis B infection.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Viread can cause side effects, although not everybody gets them.

Very common side effects

(These can affect at least 10 in every 100 patients)

- diarrhoea, being sick (vomiting), feeling sick (nausea), dizziness, rash, feeling weak

Tests may also show:

- decreases in phosphate in the blood

Common side effects

(These can affect up to 10 in every 100 patients)

- headache, stomach pain, feeling tired, feeling bloated, flatulence

Tests may also show:

- liver problems

Uncommon side effects

(These can affect up to 1 in every 100 patients)

- pain in the tummy (abdomen) caused by inflammation of the pancreas
- breakdown of muscle, muscle pain or weakness

Tests may also show:

- decreases in potassium in the blood
- increased creatinine in your blood
- pancreas problems

The breakdown of muscle, softening of the bones (with bone pain and sometimes resulting in fractures), muscle pain, muscle weakness and decreases in potassium or phosphate in the blood may occur due to damage to kidney tubule cells.

Rare side effects

(These can affect up to 1 in every 1,000 patients)

- excess lactic acid in the blood (lactic acidosis, a serious side effect that can be fatal). The following side effects may be signs of lactic acidosis:
 - deep rapid breathing
 - drowsiness
 - feeling sick (nausea), being sick (vomiting) and stomach pain

If you think you may have lactic acidosis, contact your doctor immediately.

- pain in the tummy (abdomen) caused by inflammation of the liver
- softening of the bones (with bone pain and sometimes resulting in fractures)
- inflammation of the kidney, passing a lot of urine and feeling thirsty, damage to kidney tubule cells
- changes to your urine and back pain caused by kidney problems, including kidney failure
- swelling of the face, lips, tongue or throat
- fatty liver

Other possible effects

In the treatment of HIV, combination antiretroviral therapy (including Viread) may change your body shape, by changing the way body fat is distributed. You may lose fat from your legs, arms and face; gain fat around the tummy (abdomen) and internal organs; get larger breasts or fatty lumps on the back of the neck ('buffalo hump'). The cause and the long-term effects of these changes are not yet known.

In the treatment of HIV, combination antiretroviral therapy may also cause increased fats in the blood (hyperlipaemia) and resistance to insulin. Your doctor will test for these changes.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

5. HOW TO STORE VIREAD

Keep out of the reach and sight of children.

Do not use Viread after the expiry date which is stated on the bottle and carton after {EXP}. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Viread contains

- **The active substance is** tenofovir. Each Viread tablet contains 245 mg of tenofovir disoproxil (in the form of 300 mg tenofovir disoproxil fumarate), equivalent to 136 mg of tenofovir.
- **The other ingredients are** microcrystalline cellulose (E460), pregelatinised starch (gluten free), croscarmellose sodium, lactose monohydrate, and magnesium stearate (E572) which make up the tablet core, and lactose monohydrate, hypromellose (E464), titanium dioxide (E171), glycerol triacetate (E1518) and indigo carmine aluminium lake (E132) which make up the tablet coating.

What Viread looks like and contents of the pack

Viread 245 mg film-coated tablets are almond-shaped and light blue in colour. The tablets are marked on one side with “GILEAD” and “4331” and on the other side with “300”. Viread 245 mg film-coated tablets are supplied in bottles containing 30 tablets.

The following pack sizes are available: outer cartons containing 1 x 30 film-coated tablet and 3 x 30 film-coated tablet bottles. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Gilead Sciences International Limited
Cambridge
CB21 6GT
United Kingdom

Manufacturer:
Gilead Sciences Limited
Unit 13, Stillorgan Industrial Park
Blackrock
County Dublin
Ireland

or

Nycomed Oranienburg GmbH
Lehnitzstrasse 70-98
D-16515 Oranienburg
Germany

or

Gilead Sciences Limited
IDA Business & Technology Park
Carrigtohill
County Cork
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien

Gilead Sciences Belgium BVBA
Tél/Tel: + 32 (0) 24 01 35 79

Luxembourg/Luxemburg

Gilead Sciences Belgium BVBA
Tél/Tel: + 32 (0) 24 01 35 79

България

Gilead Sciences International Ltd
Тел.: + 44 (0) 20 7136 8820

Magyarország

Gilead Sciences International Ltd
Tel: + 44 (0) 20 7136 8820

Česká republika

Gilead Sciences International Ltd
Tel: + 44 (0) 20 7136 8820

Malta

Gilead Sciences International Ltd
Tel: + 44 (0) 20 7136 8820

Danmark

Gilead Sciences Sweden AB
Tlf: + 46 (0) 8 5057 1849

Nederland

Gilead Sciences Netherlands B.V.
Tel: + 31 (0) 20 718 3698

Deutschland

Gilead Sciences GmbH
Tel: + 49 (0) 89 899890-0

Norge

Gilead Sciences Sweden AB
Tlf: + 46 (0) 8 5057 1849

Eesti

Gilead Sciences International Ltd
Tel: + 44 (0) 20 7136 8820

Österreich

Gilead Sciences GesmbH
Tel: + 43 1 260 830

Ελλάδα

Gilead Sciences Ελλάς Μ.ΕΠΕ.
Τηλ: + 30 210 8930 100

Polska

Gilead Sciences International Ltd
Tel: + 44 (0) 20 7136 8820

España

Gilead Sciences, S.L.
Tel: + 34 91 378 98 30

Portugal

Gilead Sciences, Lda.
Tel: + 351 21 7928790

France

Gilead Sciences
Tél: + 33 (0) 1 42 73 70 70

România

Gilead Sciences International Ltd
Tel: + 44 (0) 20 7136 8820

Ireland

Gilead Sciences Ltd
Tel: + 44 (0) 1223 897555

Ísland

Gilead Sciences Sweden AB
Sími: + 46 (0) 8 5057 1849

Italia

Gilead Sciences S.r.l.
Tel: + 39 02 439201

Κύπρος

Gilead Sciences Ελλάς Μ.ΕΠΕ.
Τηλ: + 30 210 8930 100

Latvija

Gilead Sciences International Ltd
Tel: + 44 (0) 20 7136 8820

Lietuva

Gilead Sciences International Ltd
Tel: + 44 (0) 20 7136 8820

Slovenija

Gilead Sciences International Ltd
Tel: + 44 (0) 20 7136 8820

Slovenská republika

Gilead Sciences International Ltd
Tel: + 44 (0) 20 7136 8820

Suomi/Finland

Gilead Sciences Sweden AB
Puh/Tel: + 46 (0) 8 5057 1849

Sverige

Gilead Sciences Sweden AB
Tel: + 46 (0) 8 5057 1849

United Kingdom

Gilead Sciences Ltd
Tel: + 44 (0) 1223 897555

This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency (EMA) web site: <http://www.ema.europa.eu/>.