Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tenofovir disoproxil Rowex 245 mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 245 mg of tenofovir disoproxil.

Excipient(s) with known effect
Each tablet contains 220 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White coloured, almond shaped, biconvex, film coated tablets, of dimensions 16 mm x 10 mm, debossed with 'H' on one side and 'T11' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

HIV-1 infection
Tenofovir disoproxil Rowex 245 mg film-coated tablets are indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected adults.

In adults, the demonstration of the benefit of tenofovir disoproxil in HIV-1 infection is based on results of one study in treatment-naïve patients, including patients with a high viral load (> 100,000 copies/ml) and studies in which tenofovir disoproxil 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).

Tenofovir disoproxil Rowex 245 mg film-coated tablets are also indicated for the treatment of HIV-1 infected adolescents, with NRTI resistance or toxicities precluding the use of first line agents, aged 12 to < 18 years.

The choice of Tenofovir disoproxil Rowex 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
Tenofovir disoproxil Rowex 245 mg film-coated tablets are indicated for the treatment of chronic hepatitis B in adults with:

- compensated liver disease, with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis (see section 5.1).
- evidence of lamivudine-resistant hepatitis B virus (see sections 4.8 and 5.1).
- decompensated liver disease (see sections 4.4, 4.8 and 5.1).

Tenofovir disoproxil Rowex 245 mg film-coated tablets are indicated for the treatment of chronic hepatitis B in adolescents 12 to < 18 years of age with:

- compensated liver disease and evidence of immune active disease, i.e. active viral replication and persistently elevated serum ALT levels or histological evidence of moderate to severe inflammation and/or fibrosis. With respect to the decision to initiate treatment in paediatric patients, see sections 4.2, 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.

Posology
HIV-1 and Chronic hepatitis B

Adults and adolescents aged 12 to < 18 years and weighing ≥ 35 kg:
The recommended dose of Tenofovir disoproxil Rowex for the treatment of HIV or for the treatment of chronic hepatitis B is 245 mg (one tablet) once daily taken orally with food.

The decision to treat paediatric patients (adolescents) should be based on careful consideration of individual patient needs and with reference to current paediatric treatment guidelines including the value of baseline histological information. The benefits of long-term virologic suppression with continued therapy must be weighed against the risk of prolonged treatment, including the emergence of resistant hepatitis B virus and the uncertainties as regards the long term impact of bone and renal toxicity (see section 4.4).

Serum ALT should be persistently elevated for at least 6 months prior to treatment of paediatric patients with compensated liver disease due to HBeAg positive chronic hepatitis B; and for at least 12 months in patients with HBeAg negative disease.

Duration of therapy in adult and adolescent patients with 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 12 months after HBe seroconversion (HBeAg loss and HBV DNA loss with anti-HBe detection on two consecutive serum samples at least 3-6 months apart) 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. Treatment discontinuation may also be considered after stable virological suppression is achieved (i.e. for at least 3 years) provided serum ALT and HBV DNA levels are followed regularly after treatment discontinuation to detect any late virological relapse. With prolonged treatment for more than 2 years, regular reassessment is recommended to confirm that continuing the selected therapy remains appropriate for the patient.

In adult patients with decompensated liver disease or cirrhosis, treatment cessation is not recommended.

Paediatric population
Tenofovir disoproxil may also be available as other formulations for the treatment of HIV-1 infection and chronic hepatitis B paediatric patients aged 2 to < 12 years and as reduced tablet strengths for the treatment of HIV-1 infection and chronic hepatitis B in paediatric patients aged 6 to < 12 years (see section 5.1). Please refer to the accompanying Summary of Product Characteristics of suitable formulations).

The safety and efficacy of tenofovir disoproxil in HIV-1 infected children or children with chronic hepatitis B under 2 years of age have not been established. No data are available.

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

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

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

Renal impairment

Tenofovir is eliminated by renal excretion and the exposure to tenofovir increases in patients with renal dysfunction.

Adults
There are limited data on the safety and efficacy of tenofovir disoproxil in adult 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 adult patients with renal impairment tenofovir disoproxil should only be used if the potential benefits of treatment are considered to outweigh the potential risks. Administration of other formulations of tenofovir disoproxil to provide a reduced daily dose of tenofovir disoproxil is recommended for adult patients with creatinine clearance < 50 ml/min, including haemodialysis patients. Please refer to the Summary of Product Characteristics of suitable formulations.

Mild renal impairment (creatinine clearance 50-80 ml/min)
Limited data from clinical studies support once daily dosing of 245 mg tenofovir disoproxil in patients with mild renal impairment.

Moderate renal impairment (creatinine clearance 30-49 ml/min)
For patients unable to take other available formulations such as granule formulation of tenofovir disoproxil, prolonged dose intervals using the 245 mg film-coated tablets may be used. Administration of 245 mg tenofovir disoproxil every 48 hours can be used based on modelling of single-dose pharmacokinetic data in HIV negative 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
For patients unable to take other available formulations such as granule formulation of tenofovir disoproxil and with no alternative treatment available, prolonged dose intervals using the 245 mg film-coated tablets may be used as follows:

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

Haemodialysis patients: 245 mg tenofovir disoproxil may be administered every 7 days following completion of a haemodialysis session*.

These dose interval adjustments have not been confirmed in clinical studies. Simulations suggest that the prolonged dose interval using Tenofovir disoproxil Rowex 245 mg film-coated tablets 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.

Paediatrics
The use of tenofovir disoproxil is not recommended in paediatric patients with renal impairment (see section 4.4).

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

If Tenofovir disoproxil Rowex 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).

Method of administration
Tenofovir disoproxil Rowex tablets should be taken once daily, orally with food.

A granules formulation of tenofovir disoproxil may be available for patients having difficulty in swallowing film-coated tablets. Please refer to the Summary of Product Characteristics of suitable formulations.

However, in exceptional circumstances Tenofovir disoproxil Rowex 245 mg film-coated tablets can be administered following disintegration of the tablet in at least 100 ml of water, orange juice or grape juice.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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

HIV-1
While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

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

Co-administration of other medicinal products

- Tenofovir disoproxil Rowex should not be administered concomitantly with other medicinal products containing tenofovir disoproxil or tenofovir alafenamide.
- Tenofovir disoproxil Rowex should not be administered concomitantly with adefovir dipivoxil.
- Co-administration of tenofovir disoproxil and didanosine is not recommended (see section 4.5).

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

Renal and bone effects in adult population
Renal effects
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 in clinical practice (see section 4.8).

Renal monitoring
It is recommended that creatinine clearance is calculated in all patients prior to initiating therapy with tenofovir disoproxil and renal function (creatinine clearance and serum phosphate) is also monitored after two to four weeks of treatment, after three months of treatment and every three to six months thereafter in patients without renal risk factors. In patients at risk for renal impairment, a more frequent monitoring of renal function is required.

Renal management
If serum phosphate is < 1.5 mg/dl (0.48 mmol/l) or creatinine clearance is decreased to < 50 ml/min in any adult patient receiving tenofovir disoproxil, 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 in adult patients with creatinine clearance decreased to < 50 ml/min or decreases in serum phosphate to < 1.0 mg/dl (0.32 mmol/l). Interrupting treatment with tenofovir disoproxil should also be considered in case of progressive decline of renal function when no other cause has been identified.

Co-administration and risk of renal toxicity
Use of tenofovir disoproxil 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 and nephrotoxic agents is unavoidable, renal function should be monitored weekly.

Cases of acute renal failure after initiation of high dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs) have been reported in patients treated with tenofovir disoproxil and with risk factors for renal dysfunction. If tenofovir disoproxil is

co-administered with an NSAID, renal function should be monitored adequately.

A higher risk of renal impairment has been reported in patients receiving tenofovir disoproxil in combination with a ritonavir or cobicistat boosted protease inhibitor. A close monitoring of renal function is required in these patients (see section 4.5). In patients with renal risk factors, the co-administration of tenofovir disoproxil with a boosted protease inhibitor should be carefully evaluated.

Tenofovir disoproxil 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).

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

Adult patients with creatinine clearance < 50 ml/min, including haemodialysis patients:

There are limited data on the safety and efficacy of tenofovir disoproxil in patients with impaired renal function. Therefore, tenofovir disoproxil should only be used if the potential benefits of treatment are considered to outweigh the potential risks. In patients with severe renal impairment (creatinine clearance < 30 ml/min) and in patients who require haemodialysis use of tenofovir disoproxil 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).

Bone effects
In HIV infected patients, in a 144-week controlled clinical study that compared tenofovir disoproxil with stavudine in combination with lamivudine and efavirenz in antiretroviral-naïve adult patients, small decreases in bone mineral density (BMD) of the hip and spine were observed in both treatment groups. Decreases in BMD of spine and changes in bone biomarkers from baseline were significantly greater in the tenofovir disoproxil treatment group at 144 weeks. Decreases in BMD of hip were significantly greater in this group until 96 weeks. However, there was no increased risk of fractures or evidence for clinically relevant bone abnormalities over 144 weeks.

In other studies (prospective and cross-sectional), the most pronounced decreases in BMD were seen in patients treated with tenofovir disoproxil as part of a regimen containing a boosted protease inhibitor. Alternative treatment regimens should be considered for patients with osteoporosis that are at a high risk for fractures.

Bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy (see section 4.8).

If bone abnormalities are suspected or detected then appropriate consultation should be obtained.

<u>Renal and bone effects in paediatric population</u>
There are uncertainties associated with the long term effects of bone and renal toxicity. Moreover, the reversibility of renal toxicity cannot be fully ascertained. Therefore, a multidisciplinary approach is recommended to adequately weigh on a case by case basis the benefit/risk balance of treatment, decide the appropriate monitoring during treatment (including decision for treatment withdrawal) and consider the need for supplementation.

Renal effects
Renal adverse reactions consistent with proximal renal tubulopathy have been reported in HIV-1 infected paediatric patients aged 2 to < 12 years in clinical study GS-US-104-0352 (see sections 4.8 and 5.1).

Renal monitoring
Renal function (creatinine clearance and serum phosphate) should be evaluated prior to treatment, and monitored during treatment as in adults (see above).

Renal management
If serum phosphate is confirmed to be < 3.0 mg/dl (0.96 mmol/l) in any paediatric patient receiving tenofovir disoproxil, 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). If renal abnormalities are suspected or detected then consultation with a nephrologist should be obtained to consider interruption of tenofovir disoproxil treatment.

Interrupting treatment with tenofovir disoproxil should also be considered in case of progressive decline of renal function when no other cause has been identified.

Co-administration and risk of renal toxicity
The same recommendations apply as in adults (see above).

Renal impairment
The use of tenofovir disoproxil is not recommended in paediatric patients with renal impairment (see section 4.2). Tenofovir disoproxil should not be initiated in paediatric patients with renal impairment and should be discontinued in paediatric patients who develop renal impairment during tenofovir disoproxil therapy.

Bone effects
Tenofovir disoproxil Rowex may cause a reduction in BMD. The effects of tenofovir disoproxil -associated changes in BMD on long-term bone health and future fracture risk are currently unknown (see section 5.1).

If bone abnormalities are detected or suspected in paediatric patients, consultation with an endocrinologist and/or nephrologist 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 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-ups 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 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 (CART) 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.

Use with certain hepatitis C virus antiviral agents

Co-administration of tenofovir disoproxil with ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir has been shown to increase plasma concentrations of tenofovir, especially when used together with an HIV regimen containing tenofovir disoproxil and a pharmacokinetic enhancer (ritonavir or cobicistat).

The safety of tenofovir disoproxil in the setting of ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir and a pharmacokinetic enhancer has not been established. The potential risks and benefits associated with co-administration of ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir with tenofovir disoproxil given in conjunction with a boosted HIV protease inhibitor (e.g. atazanavir or darunavir) should be considered, particularly in patients at increased risk of renal dysfunction. Patients receiving ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir concomitantly with tenofovir disoproxil and a boosted HIV protease inhibitor should be monitored for adverse reactions related to tenofovir disoproxil.

Weight and metabolic parameters
An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and lifestyle. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Mitochondrial dysfunction following exposure *in utero*
Nucleos(t)ide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV negative infants exposed *in utero* and/or postnatally to nucleoside analogues; these have predominantly concerned treatment with regimens containing zidovudine. The main adverse reactions reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactataemia, hyperlipasaemia). These events have often been transitory. Late onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently unknown. These findings should be considered for any child exposed *in utero* to nucleos(t)ide analogues, who present with severe clinical findings of unknown etiology, particularly neurologic findings. 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 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 mycobacterial infections, and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Osteonecrosis
Although the aetiology 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 CART. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Elderly
Tenofovir disoproxil 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.

Tenofovir disoproxil Rowex 245 mg film-coated tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interactions

Interaction studies have only been performed in adults.

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

Concomitant use not recommended
Tenofovir disoproxil Rowex should not be administered concomitantly with other medicinal products containing tenofovir disoproxil or tenofovir alafenamide.

Tenofovir disoproxil Rowex should not be administered concomitantly with adefovir dipivoxil.

Didanosine
Co-administration of tenofovir disoproxil 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 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 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.

Other interactions
Interactions between tenofovir disoproxil and other medicinal products 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 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 245 mg tenofovir disoproxil**
ANTI-INFECTIVES		
Antiretrovirals		
Protease inhibitors		
Atazanavir/Ritonavir (300 q.d./100 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./.)	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./.)	Darunavir: No significant effect on darunavir/ritonavir PK parameters. Tenofovir: AUC: ↑ 22%	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).

	C_{min}: ↑ 37%	
NRTIs		
Didanosine	Co-administration of tenofovir disoproxil and didanosine results in a 40-60% increase in systemic exposure to didanosine.	Co-administration of tenofovir disoproxil and didanosine is not recommended (see section 4.4). Increased systemic exposure to didanosine may increase didanosine related adverse reactions. Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported. Co-administration of tenofovir disoproxil 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 therapy has been associated with reports of high rates of virological failure within several tested combinations for the treatment of HIV-1 infection
Adefovir dipivoxil	AUC: ↔ C_{max}: ↔	Tenofovir disoproxil should not be administered concurrently with adefovir dipivoxil (see section 4.4).
Entecavir	AUC: ↔ C_{max}: ↔	No clinically significant pharmacokinetic interactions when tenofovir disoproxil was co-administered with entecavir.
Hepatitis C virus antiviral agents		
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Atazanavir/Ritonavir (300 mg q.d./100 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)1	Ledipasvir: AUC: ↑ 96% Cmax: ↑ 68% Cmin: ↑ 118% Sofosbuvir: AUC: ↔ Cmax: ↔ GS-3310072: AUC: ↔ Cmax: ↔ Cmin: ↑ 42% Atazanavir: AUC: ↔ Cmax: ↔ Cmin: ↑ 63% Ritonavir: AUC: ↔ Cmax: ↔ Cmin: ↑ 45% Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↔ Cmax: ↑ 47% Cmin: ↑ 47%	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, ledipasvir/sofosbuvir and atazanavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with ledipasvir/sofosbuvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring, if other alternatives are not available (see section 4.4).
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Darunavir/Ritonavir (800 mg q.d./100 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)[1]	Ledipasvir: AUC: ↔ Cmax: ↔ Cmin: ↔ Sofosbuvir:	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, ledipasvir/sofosbuvir and darunavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with ledipasvir/sofosbuvir and a pharmacokinetic enhancer (e.g. ritonavir

	AUC: ↓ 27% Cmax: ↓ 37% GS-3310072: AUC: ↔ Cmax: ↔ Cmin: ↔ Darunavir: AUC: ↔ Cmax: ↔ Cmin: ↔ Ritonavir: AUC: ↔ Cmax: ↔ Cmin: ↑ 48% Emtricitabine: AUC: ↔ Cmax: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 50% C_{max}: ↑ 64% C_{min}: ↑ 59%	or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring, if other alternatives are not available (see section 4.4).
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Efavirenz/Emtricitabine/Tenofovi r disoproxil (600 mg/200 mg/245 mg q.d.)	Ledipasvir: AUC: ↓ 34% C_{max}: ↓ 34% C_{min}: ↓ 34% Sofosbuvir: AUC: ↔ Cmax: ↔ GS-331007[2]: AUC: ↔ Cmax: ↔ C_{min}: ↔ Efavirenz: AUC: ↔ Cmax: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ Cmax: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 98% C_{max}: ↑ 79% C_{min}: ↑ 163%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4).
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Emtricitabine/Rilpivirine/Tenofo vir disoproxil (200 mg/25 mg/245 mg q.d.)	Ledipasvir: AUC: ↔ Cmax: ↔ C_{min}: ↔	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4).

	Sofosbuvir: AUC: ↔ Cmax: ↔ GS-331007[2]: AUC: ↔ Cmax: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ Cmax: ↔ C_{min}: ↔ Rilpivirine: AUC: ↔ Cmax: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 40% Cmax: ↔ C_{min}: ↑ 91%	
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Dolutegravir (50 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ Cmax: ↔ GS-331007[2] AUC: ↔ Cmax: ↔ Cmin: ↔ Ledipasvir: AUC: ↔ Cmax: ↔ Cmin: ↔ Dolutegravir AUC: ↔ Cmax: ↔ Cmin: ↔ Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↑ 65% Cmax: ↑ 61% Cmin: ↑ 115%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4).
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Atazanavir/Ritonavir (300 mg q.d./100 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/ 245 mg q.d.)	Sofosbuvir: AUC: ↔ Cmax: ↔ GS-331007[2]: AUC: ↔ Cmax: ↔ Cmin: ↑ 42%	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, sofosbuvir/velpatasvir and atazanavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with sofosbuvir/velpatasvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established.

	Velpatasvir: AUC: ↑ 142% Cmax: ↑ 55% Cmin: ↑ 301% Atazanavir: AUC: ↔ Cmax: ↔ Cmin: ↑ 39% Ritonavir: AUC: ↔ Cmax: ↔ Cmin: ↑ 29% Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↔ Cmax: ↑ 55% Cmin: ↑ 39%	The combination should be used with caution with frequent renal monitoring (see section 4.4).
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Darunavir/Ritonavir (800 mg q.d./100 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/ 245mg q.d.)	Sofosbuvir: AUC: ↓28% Cmax: ↓ 38% GS-331007[2]: AUC: ↔ Cmax: ↔ Cmin: ↔ Velpatasvir: AUC: ↔ Cmax: ↓ 24% Cmin: ↔ Darunavir: AUC: ↔ Cmax: ↔ Cmin: ↔ Ritonavir: AUC: ↔ Cmax: ↔ Cmin: ↔ Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↑ 39% Cmax: ↑ 55% Cmin: ↑ 52%	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, sofosbuvir/velpatasvir and darunavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with sofosbuvir/velpatasvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring (see section 4.4).
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Lopinavir/Ritonavir	Sofosbuvir: AUC: ↓ 29% Cmax: ↓ 41%	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, sofosbuvir/velpatasvir and lopinavir/ritonavir may increase adverse reactions related to

(800 mg/200 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)	GS-331007[2]: AUC: ↔ Cmax: ↔ Cmin: ↔ Velpatasvir: AUC: ↔ Cmax: ↓ 30% Cmin: ↑ 63% Lopinavir: AUC: ↔ Cmax: ↔ Cmin: ↔ Ritonavir: AUC: ↔ Cmax: ↔ Cmin: ↔ Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↔ Cmax: ↑ 42% Cmin: ↔	tenofovir isoproxil, including renal disorders. The safety of tenofovir disoproxil when used with sofosbuvir/velpatasvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring (see section 4.4).
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Raltegravir (400 mg b.i.d) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ Cmax: ↔ GS-331007[2]: AUC: ↔ Cmax: ↔ Cmin: ↔ Velpatasvir: AUC: ↔ Cmax: ↔ Cmin: ↔ Raltegravir: AUC: ↔ Cmax: ↔ Cmin: ↓ 21% Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↑ 40% Cmax: ↑ 46% Cmin: ↑ 70%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4).
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) +	Sofosbuvir: AUC: ↔	Concomitant administration of sofosbuvir/velpatasvir and efavirenz is expected to decrease plasma concentrations of velpatasvir.

Efavirenz/Emtricitabine/ Tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)	Cmax: ↑ 38% GS-331007[2]: AUC: ↔ Cmax: ↔ Cmin: ↔ Velpatasvir: AUC: ↓ 53% Cmax: ↓ 47% Cmin: ↓ 57% Efavirenz: AUC: ↔ Cmax: ↔ Cmin: ↔ Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↑ 81% Cmax: ↑ 77% Cmin: ↑ 121%	Co-administration of sofosbuvir/velpatasvir with efavirenz-containing regimens is not recommended.
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Emtricitabine/Rilpivirine/ Tenofovir disoproxil (200 mg/25 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ Cmax: ↔ GS-331007[2]: AUC: ↔ Cmax: ↔ Cmin: ↔ Velpatasvir: AUC: ↔ Cmax: ↔ Cmin: ↔ Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Rilpivirine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↑ 40% Cmax: ↑ 44% Cmin: ↑ 84%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4).
Sofosbuvir/Velpatasvir/ Voxilaprevir (400 mg/100 mg/ 100 mg+100 mg q.d.)[3] + Darunavir (800 mg q.d.) + Ritonavir (100 mg q.d.) + Emtricitabine/Tenofovir disoproxil	Sofosbuvir: AUC: ↔ Cmax: ↓ 30% Cmin: N/A GS-331007[2]: AUC:	Increased plasma concentrations of tenofovir resulting from coadministration of tenofovir disoproxil, sofosbuvir/velpatasvir/voxila previr and darunavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with sofosbuvir/velpatasvir/voxila previr and a pharmacokinetic enhancer

(200 mg/245 mg q.d.)	↔ Cmax:↔ Cmin: N/A Velpatasvir: AUC: ↔ Cmax: ↔ Cmin: ↔ Voxilaprevir: AUC: ↑ 143% Cmax:↑ 72% Cmin: ↑ 300% Darunavir: AUC: ↔ Cmax: ↔ Cmin: ↓ 34% Ritonavir: AUC: ↑ 45% Cmax: ↑ 60% Cmin: ↔ Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↑ 39% Cmax: ↑ 48% Cmin: ↑ 47%	(e.g. ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring (see section 4.4).
Sofosbuvir (400 mg q.d.) + Efavirenz/Emtricitabine/Tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ C_{max}: ↓ 19% GS-331007[2]: AUC: ↔ C_{max}: ↓ 23% Efavirenz: AUC: ↔ Cmax: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ Cmax: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↑ 25% C_{min}: ↔	No dose adjustment is required.

[1.] Data generated from simultaneous dosing with ledipasvir/sofosbuvir. Staggered administration (12 hours apart) provided similar results.
[2.] The predominant circulating metabolite of sofosbuvir.
[3.] Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

Studies conducted with other medicinal products

There were no clinically significant pharmacokinetic interactions when tenofovir disoproxil 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 must be taken with food, as food enhances the bioavailability of tenofovir (see section 5.2).

4.6 Fertility, pregnancy and lactation

Pregnancy
A large amount of data on pregnant women (more than 1,000 pregnancy outcomes) indicate no malformations or foetal/neonatal toxicity associated with tenofovir disoproxil. Animal studies do not indicate reproductive toxicity (see section 5.3). The use of tenofovir disoproxil may be considered during pregnancy, if necessary.

In the literature, exposure to tenofovir disoproxil in the third trimester of pregnancy has been shown to reduce the risk of HBV transmission from mother to infant if tenofovir disoproxil is given to mothers, in addition to hepatitis B immune globulin and hepatitis B vaccine in infants.

In three controlled clinical trials, a total of 327 pregnant women with chronic HBV infection were administered tenofovir disoproxil (245 mg) once daily from 28 to 32 weeks gestation through 1 to 2 months postpartum; women and their infants were followed for up to 12 months after delivery. No safety signal has emerged from these data.

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

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

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

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.

4.8 Undesirable effects

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

HIV-1: Approximately one third of patients can be expected to experience adverse reactions following treatment with tenofovir disoproxil in combination with other antiretroviral agents. These reactions are usually mild to moderate gastrointestinal events. Approximately 1% of tenofovir disoproxil -treated adult patients discontinued treatment due to the gastrointestinal events.

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

Tabulated summary of adverse reactions

Assessment of adverse reactions for tenofovir disoproxil 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 (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 (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 adult patients with chronic hepatitis B and compensated liver disease received treatment with tenofovir disoproxil 245 mg daily (n = 426) or adefovir dipivoxil 10 mg daily (n = 215) for 48 weeks. The adverse reactions observed with continued treatment for 384 weeks were consistent with the safety profile of tenofovir disoproxil. After an initial decline of approximately -4.9 ml/min (using Cockcroft-Gault equation) or -3.9 ml/min/1.73 m^2 (using modification of diet in renal disease [MDRD] equation) after the first 4 weeks of treatment, the rate of annual decline post baseline of renal function reported in tenofovir disoproxil treated patients was -1.41 ml/min per year (using Cockcroft-Gault equation) and -0.74 ml/min/1.73 m^2 per year (using MDRD equation).

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

In the tenofovir disoproxil 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. After 168 weeks, 16% (7/45) of the tenofovir disoproxil group, 4% (2/45) of the emtricitabine plus tenofovir disoproxil group, and 14% (3/22) of the entecavir group experienced tolerability failure. Thirteen percent (6/45) of the tenofovir disoproxil group, 13% (6/45) of the emtricitabine plus tenofovir disoproxil group, and 9% (2/22) of the entecavir group had a confirmed increase in serum creatinine ≥ 0.5 mg/dl or confirmed serum phosphate of < 2 mg/dl.

At week 168, in this population of patients with decompensated liver disease, the rate of death was of 13% (6/45) in the tenofovir disoproxil group, 11% (5/45) in the emtricitabine plus tenofovir disoproxil group and 14% (3/22) in the entecavir group. The rate of hepatocellular carcinoma was 18% (8/45) in the tenofovir disoproxil group, 7% (3/45) in the emtricitabine plus tenofovir disoproxil group and 9% (2/22) in the entecavir group.

Subjects with a high baseline CPT score were at higher risk of developing serious adverse events (see section 4.4).

Patients with lamivudine-resistant chronic hepatitis B: No new adverse reactions to tenofovir disoproxil were identified from a randomised, double-blind study (GS-US-174-0121) in which 280 lamivudine-resistant patients received treatment with tenofovir disoproxil (n = 141) or emtricitabine/tenofovir disoproxil (n = 139) for 240 weeks.

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 (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) or rare (≥ 1/10,000 to < 1/1,000).

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

Frequency	**Tenofovir disoproxil**
Metabolism and nutrition disorders:	
Very common:	hypophosphataemia[1]
Uncommon:	hypokalaemia[1]
Rare:	lactic acidosis
Nervous system disorders:	
Very common:	dizziness
Common:	headache
Gastrointestinal disorders:	
Very common:	diarrhoea, vomiting, nausea

Common:	abdominal pain, abdominal distension, flatulence
Uncommon:	pancreatitis
Hepatobiliary disorders:	
Common:	increased transaminases
Rare:	hepatic steatosis, hepatitis
Skin and subcutaneous tissue disorders:	
Very common:	rash
Rare:	angioedema
Musculoskeletal and connective tissue disorders:	
Uncommon:	rhabdomyolysis[1], muscular weakness[1]
Rare:	osteomalacia (manifested as bone pain and infrequently contributing to fractures)[1, 2], myopathy[1]
Renal and urinary disorders:	
Uncommon:	increased creatinine, proximal renal tubulopathy (including Fanconi syndrome)
Rare:	acute renal failure, renal failure, acute tubular necrosis, nephritis (including acute interstitial nephritis)[2], nephrogenic diabetes insipidus
General disorders and administration site conditions:	
Very common:	asthenia
Common:	fatigue

[1] This adverse reaction may occur as a consequence of proximal renal tubulopathy. It is not considered to be causally associated with tenofovir disoproxil 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 expanded access program. The frequency category was estimated from a statistical calculation based on the total number of patients exposed to tenofovir disoproxil in randomised controlled clinical trials and the expanded access program (n = 7,319).

Description of selected adverse reactions

HIV-1 and hepatitis B:

Renal impairment

As tenofovir may cause renal damage monitoring of renal function is recommended (see sections 4.4 and 4.8 Summary of the safety profile). Proximal renal tubulopathy generally resolved or improved after tenofovir disoproxil discontinuation. However, in some patients, declines in creatinine clearance did not completely resolve despite tenofovir disoproxil discontinuation. Patients at risk of renal impairment (such as patients with baseline renal risk factors, advanced HIV disease, or patients receiving concomitant nephrotoxic medications) are at increased risk of experiencing incomplete recovery of renal function despite tenofovir disoproxil discontinuation (see section 4.4).

Lactic acidosis

Cases of lactic acidosis have been reported with tenofovir disoproxil alone or in combination with other antiretrovirals. Patients with predisposing factors such as patients with decompensated liver disease, or patients receiving concomitant medications known to induce lactic acidosis are at increased risk of experiencing severe lactic acidosis during tenofovir disoproxil treatment, including fatal outcomes.

HIV-1:

Metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).

Immune reactivation syndrome

In HIV infected patients with severe immune deficiency at the time of initiation of CART, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (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 CART. The frequency of this is unknown (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 -treated patients. ALT elevations had a median time to onset of 8 weeks, resolved with continued treatment, and, in a majority of cases, were associated with a ≥ 2 $\log_{10}$ copies/ml reduction in viral load that preceded or coincided with the ALT elevation. Periodic monitoring of hepatic function is recommended during treatment (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).

Paediatric population
HIV-1
Assessment of adverse reactions is based on two randomised trials (studies GS-US-104-0321 and GS-US-104-0352) in 184 HIV-1 infected paediatric patients (aged 2 to < 18 years) who received treatment with tenofovir disoproxil (n = 93) or placebo/active comparator (n = 91) in combination with other antiretroviral agents for 48 weeks (see section 5.1). The adverse reactions observed in paediatric patients who received treatment with tenofovir disoproxil were consistent with those observed in clinical studies of tenofovir disoproxil in adults (see section 4.8 *Tabulated summary of adverse reactions and 5.1*).

Reductions in BMD have been reported in paediatric patients. In HIV-1 infected adolescents, the BMD Z-scores observed in subjects who received tenofovir disoproxil were lower than those observed in subjects who received placebo. In HIV-1 infected children, the BMD Z-scores observed in subjects who switched to tenofovir disoproxil were lower than those observed in subjects who remained on their stavudine- or zidovudine-containing regimen (see sections 4.4 and 5.1).

In study GS-US-104-0352, 8 out of 89 paediatric patients (9.0%) exposed to tenofovir disoproxil (median tenofovir disoproxil exposure 331 weeks) discontinued study drug due to renal adverse events. Five subjects (5.6%) had laboratory findings clinically consistent with proximal renal tubulopathy, 4 of whom discontinued tenofovir disoproxil therapy. Seven patients had estimated glomerular filtration rate (GFR) values between 70 and 90 mL/min/1.73 m^2. Among them, 3 patients experienced a clinically meaningful decline in estimated GFR which improved after discontinuation of tenofovir disoproxil.

Chronic hepatitis B
Assessment of adverse reactions is based on a randomised study (study GS-US-174-0115) in 106 adolescent patients (12 to < 18 years of age) with chronic hepatitis B receiving treatment with tenofovir disoproxil 245 mg (n = 52) or placebo (n = 54) for 72 weeks and a randomised study (Study GS-US-174-0144) in 89 patients with chronic hepatitis B (2 to < 12 years of age) receiving treatment with tenofovir disoproxil (n = 60) or placebo (n = 29) for 48 weeks. The adverse reactions observed in paediatric patients who received treatment with tenofovir disoproxil were consistent with those observed in clinical studies of tenofovir disoproxil in adults (see section 4.8 Tabulated summary of adverse reactions and 5.1).

Reductions in BMD have been observed in HBV infected paediatric patients 2 to < 18 years of age. The BMD Z-scores observed in subjects who received tenofovir disoproxil were lower than those observed in subjects who received placebo (see sections 4.4 and 5.1).

Other special population(s)
Elderly
Tenofovir disoproxil 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 (see section 4.4).

Patients with renal impairment
Since tenofovir disoproxil can cause renal toxicity, close monitoring of renal function is recommended in adult patients with renal impairment treated with tenofovir disoproxil (see sections 4.2, 4.4 and 5.2). The use of tenofovir disoproxil is not recommended in paediatric patients with renal impairment (see sections 4.2 and 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance; website: www.hpra.ie

4.9 Overdose

Symptoms

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.

Management
Tenofovir can be removed by haemodialysis; the median haemodialysis clearance of tenofovir is 134 ml/min. It is not known whether tenofovir can be removed by peritoneal dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action and pharmacodynamic effects
The prodrug 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 µmol/l, tenofovir has also shown no effect on the synthesis of mitochondrial DNA or the production of lactic acid in *in vitro* assays.

Data pertaining to HIV
HIV antiviral activity in vitro: The concentration of tenofovir required for 50% inhibition (EC_{50}) of the wild-type laboratory strain HIV-1_{IIIB} is 1-6 µmol/l in lymphoid cell lines and 1.1 µmol/l against primary HIV-1 subtype B isolates in PBMCs. Tenofovir is also active against HIV-1 subtypes A, C, D, E, F, G, and O and against HIV_{BaL} in primary monocyte/macrophage cells. Tenofovir shows activity *in vitro* against HIV-2, with an EC_{50} of 4.9 µmol/l in MT-4 cells.

Resistance: Strains of HIV-1 with reduced susceptibility to tenofovir and a K65R mutation in reverse transcriptase have been selected *in vitro* and in some patients (see Clinical efficacy and safety). Tenofovir disoproxil should be avoided in antiretroviral-experienced patients with strains harbouring the K65R mutation (see section 4.4). In addition, a K70E substitution in HIV-1 reverse transcriptase has been selected by tenofovir and results in low-level reduced susceptibility to tenofovir.

Clinical studies in treatment-experienced patients have assessed the anti-HIV activity of tenofovir disoproxil 245 mg 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 therapy.

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

In study GS-99-907, 550 treatment-experienced adult patients were treated with placebo or tenofovir disoproxil 245 mg for 24 weeks. The mean baseline CD4 cell count was 427 cells/mm^3, the mean baseline plasma HIV-1 RNA was 3.4 log_{10} copies/ml (78% of patients had a viral load of < 5,000 copies/ml) and the mean duration of prior HIV treatment was 5.4 years. Baseline genotypic analysis of HIV isolates from 253 patients revealed that 94% of patients had HIV-1 resistance mutations associated with nucleoside reverse transcriptase inhibitors, 58% had mutations associated with protease inhibitors and 48% had mutations associated with non-nucleoside reverse transcriptase inhibitors.

At week 24 the time-weighted average change from baseline in log_{10} plasma HIV-1 RNA levels (DAVG24) was -0.03 log_{10} copies/ml and -0.61 log_{10} copies/ml for the placebo and tenofovir disoproxil 245 mg recipients ($p < 0.0001$). A statistically significant difference in favour of tenofovir disoproxil 245 mg was seen in the time-weighted average change from baseline at week 24 (DAVG24) for CD4 count (+13 cells/mm^3 for tenofovir disoproxil 245 mg versus -11 cells/mm^3 for placebo, p-value = 0.0008). The antiviral response to tenofovir disoproxil was durable through 48 weeks (DAVG48 was -0.57 log_{10} copies/ml,

proportion of patients with HIV-1 RNA below 400 or 50 copies/ml was 41% and 18% respectively). Eight (2%) tenofovir disoproxil 245 mg 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 versus stavudine when used in combination with lamivudine and efavirenz in HIV-1 infected adult patients naïve to antiretroviral therapy. The mean baseline CD4 cell count was 279 cells/mm^3, the mean baseline plasma HIV-1 RNA was 4.91 log_{10} copies/ml, 19% of patients had symptomatic HIV-1 infection and 18% had AIDS. Patients were stratified by baseline HIV-1 RNA and CD4 count. Forty-three percent of patients had baseline viral loads > 100,000 copies/ml and 39% had CD4 cell counts < 200 cells/ml.

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

The average change from baseline for HIV-1 RNA and CD4 count at 48 weeks of treatment was similar in both treatment groups (-3.09 and -3.09 log_{10} copies/ml; +169 and 167 cells/mm^3 in the tenofovir disoproxil 245 mg and stavudine groups, respectively). At 144 weeks of treatment, the average change from baseline remained similar in both treatment groups (-3.07 and -3.03 log_{10} copies/ml; +263 and +283 cells/mm^3 in the tenofovir disoproxil 245 mg and stavudine groups, respectively). A consistent response to treatment with tenofovir disoproxil 245 mg 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 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 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. One patient in the tenofovir disoproxil arm developed the K70E substitution in the virus. From both the genotypic and phenotypic analyses there was no evidence for other pathways of resistance to tenofovir.

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

Resistance: No HBV mutations associated with tenofovir disoproxil resistance have been identified (see Clinical efficacy and safety). In cell based assays, HBV strains expressing the rtV173L, rtL180M, and rtM204I/V mutations associated with resistance to lamivudine and telbivudine showed a susceptibility to tenofovir ranging from 0.7- to 3.4-fold that of wild-type virus. HBV strains expressing the rtL180M, rtT184G, rtS202G/I, rtM204V and rtM250V mutations associated with resistance to entecavir showed a susceptibility to tenofovir ranging from 0.6- to 6.9-fold that of wild-type virus. HBV strains expressing the adefovir-associated resistance mutations rtA181V and rtN236T showed a susceptibility to tenofovir ranging from 2.9- to 10-fold that of wild- type virus. Viruses containing the rtA181T mutation remained susceptible to tenofovir with EC_{50} values 1.5-fold that of wild-type virus.

Clinical efficacy and safety
The demonstration of benefit of tenofovir disoproxil 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 to adefovir dipivoxil in adult 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 was significantly superior to adefovir dipivoxil for the primary efficacy endpoint of complete response (defined as HBV DNA levels < 400 copies/ml and Knodell necro inflammatory score improvement of at least 2 points without worsening in Knodell fibrosis). Treatment with tenofovir disoproxil 245 mg 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 necro inflammatory 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 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 negative and HBeAg positive patients at week 48

	Study 174-0102 (HBeAg negative)		**Study 174-0103 (HBeAg positive)**	
Parameter	Tenofovir disoproxil 245 mg n = 250	Adefovir dipivoxil 10 mg n = 125	Tenofovir disoproxil 245 mg n = 176	Adefovir dipivoxil 10 mg n = 90
Completeresponse (%)[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 necro inflammatory score improvement of at least 2 points without worsening in Knodell fibrosis.
[b] Knodell necro inflammatory 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 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 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 or adefovir dipivoxil 10 mg), patients rolled over with no interruption in treatment to open-label tenofovir disoproxil. In studies GS-US-174-0102 and GS-US-174-0103, 77% and 61% of patients continued in the study through to 384 weeks, respectively. At weeks 96, 144, 192, 240, 288 and 384, viral suppression, biochemical and serological responses were maintained with continued tenofovir disoproxil treatment (see Tables 4 and 5 below).

Table 4: Efficacy parameters in compensated HBeAg negative patients at week 96, 144, 192, 240, 288 and 384 open-label treatment

	Study 174-0102 (HBeAg negative)											
Parameter[a]	Tenofovir disoproxil 245 mg n = 250						Adefovir dipivoxil 10 mg roll over to tenofovir disoproxil 245 mg n = 125					
Week	96[b]	144[e]	192[g]	240[i]	288[l]	384[o]	96[c]	144[f]	192[h]	240[j]	288[m]	384[p]
HBV DNA (%) < 400 copies/ml (< 69 IU/ml)	90	87	84	83	80	74	89	88	87	84	84	76
ALT (%) Normalised ALT[d]	72	73	67	70	68	64	68	70	77	76	74	69
Serology (%) HBeAg loss/ seroconversion	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
HBsAg loss/ seroconversion	0/0	0/0	0/0	0/0	0/0	1/1[n]	0/0	0/0	0/0	0/0[k]	1/1[n]	1/1[n]

[a] Based upon Long Term Evaluation algorithm (LTE Analysis) - Patients who discontinued the study at any time prior to week 384 due to a protocol defined endpoint, as well as those completing week 384, are included in the denominator.
[b] 48 weeks of double-blind tenofovir disoproxil followed by 48 weeks open-label.
[c] 48 weeks of double-blind adefovir dipivoxil followed by 48 weeks open-label tenofovir disoproxil.
[d] The population used for analysis of ALT normalisation included only patients with ALT above ULN at baseline.
[e] 48 weeks of double-blind tenofovir disoproxil followed by 96 weeks open-label.
[f] 48 weeks of double-blind adefovir dipivoxil followed by 96 weeks open-label tenofovir disoproxil.
[g] 48 weeks of double-blind tenofovir disoproxil followed by 144 weeks open-label.
[h] 48 weeks of double-blind adefovir dipivoxil followed by 144 weeks open-label tenofovir disoproxil.
[i] 48 weeks of double-blind tenofovir disoproxil followed by 192 weeks open-label.
[j] 48 weeks of double-blind adefovir dipivoxil followed by 192 weeks open-label tenofovir disoproxil.
[k] One patient in this group became HBsAg negative for the first time at the 240 week visit and was ongoing in the study at the time of the data cut-off. However, the subject's HBsAg loss was ultimately confirmed at the subsequent visit.
[l] 48 weeks of double-blind tenofovir disoproxil followed by 240 weeks open-label.
[m] 48 weeks of double-blind adefovir dipivoxil followed by 240 weeks open-label tenofovir disoproxil.
[n] Figures presented are cumulative percentages based upon a Kaplan Meier analysis excluding data collected after the addition of emtricitabine to open-label tenofovir disoproxil (KM- tenofovir disoproxil).
[o] 48 weeks of double-blind tenofovir disoproxil followed by 336 weeks open-label.
[p] 48 weeks of double-blind adefovir dipivoxil followed by 336 weeks open-label tenofovir disoproxil. n/a = not applicable.

Table 5: Efficacy parameters in compensated HBeAg positive patients at week 96, 144, 192, 240, 288 and 384 open-label treatment

	Study 174-0103 (HBeAg positive)											
Parameter[a]	Tenofovir disoproxil 245 mg (as) n = 176						Adefovir dipivoxil 10 mg roll over to tenofovir disoproxil 245 mg n = 90					
Week	96[b]	144[e]	192[h]	240[j]	288[m]	384[o]	96[c]	144[f]	192[i]	240[k]	288[n]	384[p]
HBV DNA (%) < 400 copies/ml (< 69 IU/ml)	76	72	68	64	61	56	74	71	72	66	65	61
ALT (%) Normalised ALT[d]	60	55	56	46	47	47	65	61	59	56	57	56
Serology (%) HBeAg loss/ seroconversion	26/ 23	29/ 23	34/ 25	38/ 30	37/ 25	30/ 20	24/ 20	33/ 26	36/ 30	38/ 31	40/ 31	35/ 24
HBsAg loss/ seroconversion	5/ 4	8/ 6[g]	11/ 8[g]	11/ 8[l]	12/ 8[l]	15/ 12[l]	6/ 5	8/ 7[g]	8/ 7[g]	10/ 10[l]	11/ 10[l]	13/ 11[l]

[a] Based upon Long Term Evaluation algorithm (LTE Analysis) - Patients who discontinued the study at any time prior to week 384 due to a protocol defined endpoint, as well as those completing week 384, are included in the denominator.
[b] 48 weeks of double-blind tenofovir disoproxil followed by 48 weeks open-label.
[c] 48 weeks of double-blind adefovir dipivoxil followed by 48 weeks open-label tenofovir disoproxil.
[d] The population used for analysis of ALT normalisation included only patients with ALT above ULN at baseline.
[e] 48 weeks of double-blind tenofovir disoproxil followed by 96 weeks open-label.
[f] 48 weeks of double-blind adefovir dipivoxil followed by 96 weeks open-label tenofovir disoproxil.
[g] Figures presented are cumulative percentages based upon a Kaplan Meier analysis including data collected after the addition of emtricitabine to open-label tenofovir disoproxil (KM-ITT).
[h] 48 weeks of double-blind tenofovir disoproxil followed by 144 weeks open-label.
[i] 48 weeks of double-blind adefovir dipivoxil followed by 144 weeks open-label tenofovir disoproxil.
[j] 48 weeks of double-blind tenofovir disoproxil followed by 192 weeks open-label.
[k] 48 weeks of double-blind adefovir dipivoxil followed by 192 weeks open-label tenofovir disoproxil.
[l] Figures presented are cumulative percentages based upon a Kaplan Meier analysis excluding data collected after the addition of emtricitabine to open-label tenofovir disoproxil (KM- tenofovir disoproxil).
[m] 48 weeks of double-blind tenofovir disoproxil followed by 240 weeks open-label.
[n] 48 weeks of double-blind adefovir dipivoxil followed by 240 weeks open-label tenofovir disoproxil.
[o] 48 weeks of double-blind tenofovir disoproxil followed by 336 weeks open-label.
[p] 48 weeks of double-blind adefovir dipivoxil followed by 336 weeks open-label tenofovir disoproxil.

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

Table 6: Histological response (%) in compensated HBeAg negative and HBeAg positive subjects at week 240 compared to baseline

	Study 174-0102 (HBeAg		**Study 174-0103 (HBeAg**	

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

[a] The population used for analysis of histology included only patients with available liver biopsy data (Missing = Excluded) by week 240. Response after addition of emtricitabine is excluded (total of 17 subjects across both studies).
[b] Knodell necro inflammatory score improvement of at least 2 points without worsening in Knodell fibrosis score.
[c] 48 weeks double-blind tenofovir disoproxil followed by up to 192 weeks open-label.
[d] 48 weeks double-blind adefovir dipivoxil followed by up to 192 weeks open-label tenofovir disoproxil.

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

Experience in patients with persistent viral replication (study GS-US-174-0106)
The efficacy and safety of tenofovir disoproxil 245 mg or tenofovir disoproxil 245 mg plus 200 mg emtricitabine has been evaluated in a randomised, double-blind study (study GS-US-174-0106), in HBeAg positive and HBeAg negative adult 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 versus 60% of patients randomised to emtricitabine plus tenofovir disoproxil treatment group had previously been treated with lamivudine. Overall at week 24, treatment with tenofovir disoproxil 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 (p = 0.672). In addition 55% (29/53) of patients treated with tenofovir disoproxil 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 (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 in HBV monoinfected patients are ongoing.

Experience in patients with decompensated liver disease at 48 weeks (study GS-US-174-0108)
Study GS-US-174-0108 is a randomised, double-blind, active controlled study evaluating the safety and efficacy of tenofovir disoproxil (n = 45), emtricitabine plus tenofovir disoproxil (n = 45), and entecavir (n = 22), in patients with decompensated liver disease. In the tenofovir disoproxil 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, and 94% (33/35) of emtricitabine plus tenofovir disoproxil 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 versus tenofovir disoproxil, (see Table 7 below).

Table 7: Safety and efficacy parameters in decompensated patients at week 48

	Study 174-0108		
Parameter	Tenofovir disoproxil	Emtricitabine 200 mg/	Entecavir

	245 mg (n = 45)	tenofovir disoproxil 245 mg (n = 45)	(0.5 mg or 1 mg) (n = 22)
Tolerability failure (permanent discontinuation of study drug due to a treatment emergent AE) 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.

Experience beyond 48 weeks in study GS-US-174-0108
Using a noncompleter/switch = failure analysis, 50% (21/42) of subjects receiving tenofovir disoproxil, 76% (28/37) of subjects receiving emtricitabine plus tenofovir disoproxil and 52% (11/21) of subjects receiving entecavir achieved HBV DNA < 400 copies/ml at week 168.

Experience in patients with lamivudine-resistant HBV at 240 weeks (study GS-US-174-0121)
The efficacy and safety of 245 mg tenofovir disoproxil was evaluated in a randomised, double-blind study (GS-US-174-0121) in HBeAg positive and HBeAg negative patients (n = 280) with compensated liver disease, viraemia (HBV DNA ≥ 1,000 IU/ml), and genotypic evidence of lamivudine resistance (rtM204I/V +/- rtL180M). Only five had adefovir-associated resistance mutations at baseline. One hundred forty-one and 139 adult subjects were randomised to a tenofovir disoproxil and emtricitabine plus tenofovir disoproxil treatment arm, respectively. Baseline demographics were similar between the two treatment arms: At baseline, 52.5% of subjects were HBeAg negative, 47.5% were HBeAg positive, mean HBV DNA level was 6.5 $\log_{10}$ copies/ml, and mean ALT was 79 U/l, respectively.

After 240 weeks of treatment, 117 of 141 subjects (83%) randomised to tenofovir disoproxil had HBV DNA < 400 copies/ml, and 51 of 79 subjects (65%) had ALT normalisation. After 240 weeks of treatment with emtricitabine plus tenofovir disoproxil, 115 of 139 subjects (83%) had HBV DNA < 400 copies/ml, and 59 of 83 subjects (71%) had ALT normalisation. Among the HBeAg positive subjects randomised to tenofovir disoproxil, 16 of 65 subjects (25%) experienced HBeAg loss, and 8 of 65 subjects (12%) experienced anti-HBe seroconversion through week 240. In the HBeAg positive subjects randomised to emtricitabine plus tenofovir disoproxil, 13 of 68 subjects (19%) experienced HBeAg loss, and 7 of 68 subjects (10%) experienced anti-HBe seroconversion through week 240. Two subjects randomised to tenofovir disoproxil experienced HBsAg loss by week 240, but not seroconversion to anti-HBs. Five subjects randomised to emtricitabine plus tenofovir disoproxil experienced HBsAg loss, with 2 of these 5 subjects experiencing seroconversion to anti-HBs.

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 initially randomised to double-blind tenofovir disoproxil treatment and then switched to open-label tenofovir disoproxil treatment were evaluated for genotypic changes in HBV polymerase from baseline. Genotypic evaluations performed on all patients with HBV DNA > 400 copies/ml at week 48 (n = 39), 96 (n = 24), 144 (n = 6), 192 (n = 5), 240 (n = 4), 288 (n = 6) and 384 (n = 2) of tenofovir disoproxil monotherapy showed that no mutations associated with tenofovir disoproxil resistance have developed.

Two hundred and fifteen HBeAg negative (GS-US-174-0102, n = 125) and HBeAg positive (GS-US-174-0103, n = 90) patients initially randomised to double-blind adefovir dipivoxil treatment and then switched to open-label tenofovir disoproxil treatment were evaluated for genotypic changes in HBV polymerase from baseline. Genotypic evaluations performed on all

patients with HBV DNA > 400 copies/ml at week 48 (n = 16), 96 (n = 5), 144 (n = 1), 192 (n = 2), 240 (n = 1), 288 (n = 1) and 384 (n = 2) of tenofovir disoproxil monotherapy showed that no mutations associated with tenofovir disoproxil 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 for up to 168 weeks. Genotypic data from paired baseline and on treatment HBV isolates were available for 6/8 patients with HBV DNA > 400 copies/ml at week 48. No amino acid substitutions associated with resistance to tenofovir disoproxil were identified in these isolates. Genotypic analysis was conducted for 5 subjects in the tenofovir disoproxil arm post week 48. No amino acid substitutions associated with tenofovir disoproxil resistance were detected in any subject.

In study GS-US-174-0121, 141 patients with lamivudine resistance substitutions at baseline received tenofovir disoproxil for up to 240 weeks. Cumulatively, there were 4 patients who experienced a viremic episode (HBV DNA>400 copies/ml) at their last timepoint ontenofovir disoproxil. Among them, sequence data from paired baseline and on treatment HBV isolates were available for 2 of 4 patients. No amino acid substitutions associated with resistance to tenofovir disoproxil were identified in these isolates.

In a paediatric study (GS-US-174-0115), 52 patients (including 6 patients with lamivudine resistance mutations at baseline) initially received blinded tenofovir disoproxil for up to 72 weeks and then 51/52 patients switched to open-label tenofovir disoproxil (tenofovir disoproxil-tenofovir disoproxil group). Genotypic evaluations were performed on all patients within this group with HBV DNA > 400 copies/ml at week 48 (n = 6), week 72 (n = 5), week 96 (n = 4), week 144 (n = 2), and week 192 (n = 3). Fifty-four patients (including 2 patients with lamivudine resistance mutations at baseline) initially received blinded placebo treatment for 72 weeks, and 52/54 patients followed with tenofovir disoproxil (PLB-tenofovir disoproxil group). Genotypic evaluations were performed on all patients within this group with HBV DNA > 400 copies/ml at week 96 (n = 17), week 144 (n = 7), and week 192 (n = 8). No amino acid substitutions associated with resistance to tenofovir disoproxil were identified in these isolates.

In a paediatric study (GS-US-174-0144), genotypic data from paired baseline and on treatment HBV isolates from patients who received tenofovir disoproxil were available for 9 of 10 patients who had plasma HBV DNA > 400 copies/ml. No amino acid substitutions associated with resistance to tenofovir disoproxil were identified in these isolates by week 48.

Paediatric population

HIV-1: In study GS-US-104-0321, 87 HIV-1 infected treatment-experienced patients 12 to < 18 years of age were treated with tenofovir disoproxil (n = 45) or placebo (n = 42) in combination with an optimised background regimen (OBR) for 48 weeks. Due to limitations of the study, a benefit of tenofovir disoproxil over placebo was not demonstrated based on plasma HIV-1 RNA levels at week 24. However, a benefit is expected for the adolescent population based on extrapolation of adult data and comparative pharmacokinetic data (see section 5.2).

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

In study GS-US-104-0352, 97 treatment-experienced patients 2 to < 12 years of age with stable, virologic suppression on stavudine- or zidovudine-containing regimens were randomised to either replace stavudine or zidovudine with tenofovir disoproxil (n = 48) or continue on their original regimen (n = 49) for 48 weeks. At week 48, 83% of patients in the tenofovir disoproxil treatment group and 92% of patients in the stavudine or zidovudine treatment group had HIV-1 RNA concentrations < 400 copies/ml. The difference in the proportion of patients who maintained < 400 copies/ml at week 48 was mainly influenced by the higher number of discontinuations in the tenofovir disoproxil treatment group. When missing data were excluded, 91% of patients in the tenofovir disoproxil treatment group and 94% of patients in the stavudine or zidovudine treatment group had HIV-1 RNA concentrations < 400 copies/ml at week 48.

Reductions in BMD have been reported in paediatric patients. In patients who received treatment with tenofovir disoproxil, or stavudine or zidovudine, mean lumbar spine BMD Z-score was -1.034 and -0.498, and mean total body BMD Z-score was -0.471 and -0.386, respectively, at baseline. Mean changes at week 48 (end of randomised phase) were 0.032 and 0.087 in lumbar spine BMD Z-score, and -0.184 and -0.027 in total body BMD Z-score for the tenofovir disoproxil and stavudine or

zidovudine groups, respectively. The mean rate of lumbar spine bone gain at week 48 was similar between the tenofovir disoproxil treatment group and the stavudine or zidovudine treatment group. Total body bone gain was less in the tenofovir disoproxil treatment group compared to the stavudine or zidovudine treatment group. One tenofovir disoproxil treated subject and no stavudine or zidovudine treated subjects experienced significant (> 4%) lumbar spine BMD loss at week 48. BMD Z-scores declined by -0.012 for lumbar spine and by -0.338 for total body in the 64 subjects who were treated with tenofovir disoproxil for 96 weeks. BMD Z-scores were not adjusted for height and weight.

In study GS-US-104-0352, 8 out of 89 paediatric patients (9.0%) exposed to tenofovir disoproxil discontinued study drug due to renal adverse events. Five subjects (5.6%) had laboratory findings clinically consistent with proximal renal tubulopathy, 4 of whom discontinued tenofovir disoproxil therapy (median tenofovir disoproxil exposure 331 weeks).

Chronic hepatitis B: In study GS-US-174-0115, 106 HBeAg negative and HBeAg positive patients aged 12 to < 18 years with chronic HBV infection [HBV DNA ≥ 105 copies/ml, elevated serum ALT (≥ 2 x ULN) or a history of elevated serum ALT levels in the past 24 months] were treated with tenofovir disoproxil 245 mg (n = 52) or placebo (n = 54) for 72 weeks. Subjects must have been naïve to tenofovir disoproxil, but could have received interferon based regimens (> 6 months prior to screening) or any other non-tenofovir disoproxil containing oral anti-HBV nucleoside/nucleotide therapy (> 16 weeks prior to screening). At week 72, overall 88% (46/52) of patients in the tenofovir disoproxil treatment group and 0% (0/54) of patients in the placebo group had HBV DNA < 400 copies/ml. Seventy-four percent (26/35) of patients in the tenofovir disoproxil group had normalised ALT at week 72 compared to 31% (13/42) in the placebo group. Response to treatment with tenofovir disoproxil was comparable in nucleos(t)ide-naïve (n = 20) and nucleos(t)ide-experienced (n = 32) patients, including lamivudine- resistant patients (n = 6). Ninety-five percent of nucleos(t)ide-naïve patients, 84% of nucleos(t)ide- experienced patients, and 83% of lamivudine-resistant patients achieved HBV DNA < 400 copies/ml at week 72. Thirty-one of the 32 nucleos(t)ide-experienced patients had prior lamivudine experience. At week 72, 96% (27/28) of immune-active patients (HBV DNA ≥ 105 copies/ml, serum ALT > 1.5 x ULN) in the tenofovir disoproxil treatment group and 0% (0/32) of patients in the placebo group had HBV DNA < 400 copies/ml. Seventy-five percent (21/28) of immune-active patients in the tenofovir disoproxil group had normal ALT at week 72 compared to 34% (11/32) in the placebo group.

After 72 weeks of blinded randomized treatment, each subject could switch to open-label tenofovir disoproxil treatment up to week 192. After week 72, virologic suppression was maintained for those receiving double-blind tenofovir disoproxil followed by open-label tenofovir disoproxil (tenofovir disoproxil-tenofovir disoproxil group): 86.5% (45/52) of subjects in the tenofovir disoproxil-tenofovir disoproxil group had HBV DNA < 400 copies/ml at week 192. Among the subjects who received placebo during the double-blind period, the proportion of subjects with HBV DNA < 400 copies/mL rose sharply after they began treatment with open-label tenofovir disoproxil (PLB- tenofovir disoproxil group): 74.1% (40/54) of subjects in the PLB- tenofovir disoproxil group had HBV DNA < 400 copies/ml at week 192. The proportion of subjects with ALT normalization at week 192 in the tenofovir disoproxil-tenofovir disoproxil group was 75.8% (25/33) among those who were HBeAg positive at baseline and 100.0% (2 of 2 subjects) among those who were HBeAg negative at baseline. Similar percentages of subjects in the tenofovir disoproxil-tenofovir disoproxil and PLB- tenofovir disoproxil groups (37.5% and 41.7%, respectively) experienced seroconversion to anti-HBe through week 192.

Bone Mineral Density (BMD) data from Study GS-US-174-0115 are summarized in Table 8:

Table 8: Bone Mineral Density Evaluation at Baseline, Week 72 and 192

	Baseline		**Week 72**		**Week 192**	
	Tenofovir disoproxil-tenofovir disoproxil	**PLB-tenofovir disoproxil**	**Tenofovir disoproxil-tenofovir disoproxil**	**PLB-tenofovir disoproxil**	**Tenofovir disoproxil-tenofovir disoproxil**	**PLB-tenofovir disoproxil**
Lumbar spine mean (SD) BMD Z-score[a]	−0.42 (0.762)	-0.26 (0.806)	-0.49 (0.852)	-0.23 (0.893)	-0.37 (0.946)	-0.44 (0.920)
Lumbar spine mean (SD) change from baseline BMD Z-score[a]	NA	NA	-0.06 (0.320)	0.10 (0.378)	0.02 (0.548)	-0.10 (0.543)
Whole body mean (SD) BMD Z-score[a]	−0.19 (1.110)	−0.23 (0.859)	−0.36 (1.077)	−0.12 (0.916)	−0.38 (0.934)	−0.42 (0.942)
Whole body mean (SD) change from baseline BMD Z-score[a]	NA	NA	−0.16 (0.355)	0.09 (0.349)	-0.16 (0.521)	-0.19 (0.504)
Lumbar spine BMD at least 6% decreaseb	NA	NA	1.9% (1 subject)	0%	3.8% (2 subjects)	3.7% (2 subjects)

Whole body BMD at least 6% decreaseb	NA	NA	0%	0%	0%	1.9% (1 subject)
Lumbar spine BMD mean % increase	NA	NA	5.14%	8.08%	10.05%	11.21%
Whole body BMD mean % increase	NA	NA	3.07%	5.39%	6.09%	7.22%

NA = Not Applicable
[a] BMD Z-scores not adjusted for height and weight [b] Primary safety endpoint through week 72

In study GS-US-174-0144, 89 HBeAg-negative and -positive patients aged 2 to < 12 years with chronic hepatitis B were treated with tenofovir disoproxil 6.5 mg/kg up to a maximum dose of 245 mg (n = 60) or placebo (n = 29) once daily for 48 weeks. Subjects must have been naïve to tenofovir disoproxil, with HBV DNA > 105 copies/mL (~ 4.2 log10 IU/mL) and ALT >1.5 × the upper limit of normal (ULN) at screening. At Week 48, 77% (46 of 60) of patients in the tenofovir disoproxil treatment group and 7% (2 of 29) of patients in the placebo group had HBV DNA < 400 copies/mL (69 IU/mL). Sixty-six percent (38 of 58) of patients in the tenofovir disoproxil group had normalized ALT at week 48 compared with 15% (4 of 27) in the placebo group. Twenty-five percent (14 of 56) of patients in the tenofovir disoproxil group and 24% (7 of 29) of patients in the placebo group achieved HBeAg seroconversion at Week 48.

Response to treatment with tenofovir disoproxil was comparable in treatment-naïve and treatment experienced subjects with 76% (38/50) of treatment-naïve and 80% (8/10) of treatment-experienced subjects achieving HBV DNA < 400 copies/mL (69 IU/ml) at Week 48. Response to treatment with tenofovir disoproxil was also similar in subjects who were HBeAg-negative compared with those who were HBeAg-positive at baseline with 77% (43/56) HBeAg-positive and 75.0% (3/4) HBeAg-negative subjects achieving HBV DNA < 400 copies/mL (69 IU/mL) at Week 48. The distribution of HBV genotypes at baseline was similar between the TDF and Placebo groups. The majority of subjects were either genotypes C (43.8%) or D (41.6%) with a lower and similar frequency of genotypes A and B (6.7% each). Only 1 subject randomized to the TDF group was genotype E at baseline. In general, treatment responses to tenofovir disoproxil were similar for genotypes A, B, C and E [75-100% of subjects achieved HBV DNA < 400 copies/mL (69 IU/mL) at Week 48] with a lower response rate in subjects with genotype D infection (55%).
Bone Mineral Density (BMD) data from Study GS-US-174-0144 are summarized in Table 9:

Table 9: Bone Mineral Density Evaluation at Baseline and Week 48

	Base	**line**	**Week 48**	
	TDF	**PLB**	**TDF**	**PLB**
Lumbar spine mean (SD) BMD Z-score[a]	0.02 (0.977)	-0.29 (1.229)	-0.11 (0.983)	-0.11 (1.234)
Lumbar spine mean (SD) change from baseline BMD Z-score[a]	NA	NA	-0.12 (0.411)	0.14 (0.330)
Whole body mean (SD) BMD Z-score[a]	0.11 (0.743)	−0.05 (1.497)	-0.34 (0.939)	0.20 (1.299)
Whole body mean (SD) change from baseline BMD Z-scorea	NA	NA	−0.18 (0.334)	0.22 (0.446)
Lumbar spine BMD at least 4% decrease[b]	NA	NA	18.3% (11 subjects)	6.9% (2 subjects)
Whole body BMD at least 4% decrease	NA	NA	6.7% (4 subjects)	0%
Lumbar spine BMD mean % increase[b]	NA	NA	3.8%	7.6%
Whole body BMD mean % increase	NA	NA	4.5%	8.9%

NA = Not Applicable
[a] BMD Z-scores only available for a limited set of subjects with matched reference data [b] Secondary endpoint through week 48

The European Medicines Agency has deferred the obligation to submit the results of studies with tenofovir disoproxil in one or more subsets of the paediatric population in HIV and chronic hepatitis B (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Tenofovir disoproxil 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 to HIV infected patients, tenofovir disoproxil is rapidly absorbed and converted to tenofovir. Administration of multiple doses of tenofovir disoproxil with a meal to HIV infected patients resulted in

mean (%CV) tenofovir C_{max}, AUC, 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 in fasted patients was approximately 25%. Administration of tenofovir disoproxil 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 in fed patients, the median C_{max} in serum ranged from 213 to 375 ng/ml. However, administration of tenofovir disoproxil 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, 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 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 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 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 dose over the dose range 75 to 600 mg and were not affected by repeated dosing at any dose level.

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

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

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

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

Chronic hepatitis B: Steady-state tenofovir exposure in HBV infected adolescent patients
(12 to < 18 years of age) receiving an oral daily dose of tenofovir disoproxil 245 mg was similar to exposures achieved in adults receiving once-daily doses of tenofovir disoproxil 245 mg.

Tenofovir exposure in HBV infected paediatric patients 2 to <12 years of age receiving an oral daily dose of tenofovir disoproxil 6.5 mg/kg of body weight (tablet or granules) up to a maximum dose of 245 mg was similar to exposures achieved in HIV-1

infected paediatric patients 2 to <12 years of age receiving a once daily dose of tenofovir disoproxil 6.5 mg/kg up to a maximum dose of tenofovir disoproxil 245 mg.

Pharmacokinetic studies have not been performed with tenofovir disoproxil 245 mg tablets in children under 12 years or with renal impairment.

Renal impairment
Pharmacokinetic parameters of tenofovir were determined following administration of a single dose of tenofovir disoproxil 245 mg to 40 non-HIV, non-HBV infected adult 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 is modified in adult 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.

The pharmacokinetics of tenofovir in paediatric patients with renal impairment have not been studied. No data are available to make dose recommendations (see sections 4.2 and 4.4).

Hepatic impairment
A single 245 mg dose of tenofovir disoproxil was administered to non-HIV, non-HBV infected adult patients with varying degrees of hepatic impairment defined according to Child-Pugh-Turcotte (CPT) classification. Tenofovir pharmacokinetics were not substantially altered in subjects with hepatic impairment suggesting that no dose adjustment is required in these subjects. The mean (%CV) tenofovir C_{max} and $AUC_{0-\infty}$ values were 223 (34.8%) ng/ml and 2,050 (50.8%) ng·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

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

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

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

Reproductive studies in rats and rabbits showed no effects on mating, fertility, pregnancy or foetal parameters. However, tenofovir disoproxil reduced the viability index and weight of pups in peri-postnatal toxicity studies at maternally toxic doses.

The active substance tenofovir disoproxil and its main transformation products are persistent in the environment.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Cellulose, microcrystalline
Lactose monohydrate
Starch, pregelatinised (maize)
Crospovidone (Type B)
Magnesium stearate

Film-coating
Hypromellose
Titanium Dioxide (E171)
Macrogol 400
Polysorbate 80

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

After first opening of the bottle: 30 days.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Push-through OPA-Al-PVC/Al unit-dose blister
Pack sizes: 30x1, 60x1 and 90x1 film-coated tablets.

White opaque colour HDPE bottle, containing a silica gel desiccant canister and purified rayon coils, with a white opaque polypropylene child resistant screw cap.
Pack sizes: 30, 60 (2x30) and 90 (3x30) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Newtown

Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/260/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31st March 2017

10 DATE OF REVISION OF THE TEXT

October 2020