Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ictastan 200 mg/245 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 mg of emtricitabine and 245 mg of tenofovir disoproxil (equivalent to 300.6 mg of tenofovir disoproxil succinate).

Excipient with known effect:
Each tablet contains 96 mg lactose monohydrate.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Blue coloured, capsule shaped film-coated tablets, plain on both sides. The dimensions of the tablets are 19.3 mm x 8.8 mm ± 5%.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Ictastan is a fixed dose combination of emtricitabine and tenofovir disoproxil succinate. It is indicated in antiretroviral combination therapy for the treatment of HIV-1 infected adults aged 18 years and over.
The demonstration of the benefit of the combination emtricitabine and tenofovir disoproxil in antiretroviral therapy is based solely on studies performed in treatment-naïve patients (see section 5.1).

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the management of HIV infection.

Posology
Adults: The recommended dose of Ictastan is one tablet, taken orally, once daily. In order to optimise the absorption of tenofovir, it is recommended that Ictastan should be taken with food. Even a light meal improves absorption of tenofovir from the combination tablet (see section 5.2).

Where discontinuation of therapy with one of the components of Ictastan is indicated or where dose modification is necessary, separate preparations of emtricitabine and tenofovir disoproxil are available. Please refer to the Summary of Product Characteristics for these medicinal products.

If a patient misses a dose of Ictastan within 12 hours of the time it is usually taken, the patient should take Ictastan with food as soon as possible and resume their normal dosing schedule. If a patient misses a dose of Ictastan 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 Ictastan, another tablet should be taken. If the patient vomits more than 1 hour after taking Ictastan 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. However, no adjustment in the recommended daily dose for adults should be required unless there is evidence of renal insufficiency.

Renal impairment: Emtricitabine and tenofovir are eliminated by renal excretion and the exposure to emtricitabine and tenofovir increases in patients with renal dysfunction. There are limited data on the safety and efficacy of emtricitabine and tenofovir disoproxil in patients with moderate and severe renal impairment (creatinine clearance < 50 ml/min) and long-term

safety data has not been evaluated for mild renal impairment (creatinine clearance 50-80 ml/min). Therefore, in patients with renal impairment emtricitabine and tenofovir disoproxil should only be used if the potential benefits of treatment are considered to outweigh the potential risks. Patients with renal impairment may require close monitoring of renal function (see section 4.4). Dose interval adjustments are recommended for patients with creatinine clearance between 30 and 49 ml/min. These dose adjustments have not been confirmed in clinical studies and the clinical response to treatment should be closely monitored in these patients (see sections 4.4 and 5.2).

Mild renal impairment (creatinine clearance50-80 ml/min): Limited data from clinical studies support once daily dosing of emtricitabine and tenofovir disoproxil in patients with mild renal impairment (see section 4.4).

Moderate renal impairment (creatinine clearance30-49 ml/min): Administration of emtricitabine and tenofovir disoproxil every 48 hours is recommended, based on modelling of single-dose pharmacokinetic data for emtricitabine and tenofovir disoproxil in non-HIV infected subjects with varying degrees of renal impairment (see section 4.4).

Severe renal impairment (creatinine clearance<30 ml/min) and haemodialysis patients: Emtricitabine and tenofovir disoproxil is not recommended for patients with severe renal impairment (creatinine clearance < 30 ml/min) and in patients who require haemodialysis because appropriate dose reductions cannot be achieved with the combination tablet.

Hepatic impairment: The pharmacokinetics of emtricitabine and tenofovir disoproxil and emtricitabine have not been studied in patients with hepatic impairment. The pharmacokinetics of tenofovir have been studied in patients with hepatic impairment and no dose adjustment is required for tenofovir disoproxil in these patients. Based on minimal hepatic metabolism and the renal route of elimination for emtricitabine, it is unlikely that a dose adjustment would be required for emtricitabine and tenofovir disoproxil in patients with hepatic impairment (see sections 4.4 and 5.2).

If emtricitabine and tenofovir disoproxil is discontinued in patients co-infected with HIV and hepatitis B virus (HBV), these patients should be closely monitored for evidence of exacerbation of hepatitis (see section 4.4).

Paediatric population: The safety and efficacy of emtricitabine and tenofovir disoproxil in children under the age of 18 years have not been established (see section 5.2).

Method of administration
Ictastan tablets should be taken once daily, orally with food.

If patients have difficulty in swallowing, Ictastan can be crushed and then dispersed in at least 100 ml of water, orange juice or grape juice and taken immediately.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Co-administration of other medicinal products

Ictastan should not be administered concomitantly with other medicinal products containing emtricitabine, tenofovir disoproxil or other cytidine analogues, such as lamivudine (see section 4.5). Ictastan should not be administered concomitantly with adefovir dipivoxil.

Co-administration of tenofovir disoproxil and didanosine: Is not recommended.

Triple nucleoside therapy
There have been reports of a high rate of virological failure and of emergence of resistance at an early stage when tenofovir disoproxil was combined with lamivudine and abacavir as well as with lamivudine and didanosine as a once daily regimen. There is close structural similarity between lamivudine and emtricitabine and similarities in the pharmacokinetics and pharmacodynamics of these two agents. Therefore, the same problems may be seen if emtricitabine and tenofovir disoproxil is administered with a third nucleoside analogue.

Opportunistic infections

Patients receiving emtricitabine and tenofovir disoproxil or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with HIV associated diseases.

Transmission of HIV
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.

Renal impairment
Emtricitabine and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. Renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir disoproxil in clinical practice (see section 4.8).

It is recommended that creatinine clearance is calculated in all patients prior to initiating therapy with emtricitabine and 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.

Patients with renal impairment (creatinine clearance<80 ml/min), including haemodialysis patients: Renal safety with emtricitabine and tenofovir disoproxil has only been studied to a very limited degree in patients with impaired renal function (creatinine clearance < 80 ml/min). Dose interval adjustments are recommended for patients with creatinine clearance 30-49 ml/min (see section 4.2). Limited clinical study data suggest that the prolonged dose interval is not optimal and could result in increased toxicity and possibly inadequate response. Furthermore, in a small clinical study, a subgroup of patients with creatinine clearance between 50 and 60 ml/min who received tenofovir disoproxil in combination with emtricitabine every 24 hours had a 2-4-fold higher exposure to tenofovir and worsening of renal function (see section 5.2). Therefore, a careful benefit-risk assessment is needed when emtricitabine and tenofovir disoproxil is used in patients with creatinine clearance < 60 ml/min, and renal function should be closely monitored. In addition, the clinical response to treatment should be closely monitored in patients receiving emtricitabine and tenofovir disoproxil at a prolonged dosing interval. The use of emtricitabine and tenofovir disoproxil is not recommended in patients with severe renal impairment (creatinine clearance < 30 ml/min) and in patients who require haemodialysis since appropriate dose reductions cannot be achieved with the combination tablet (see sections 4.2 and 5.2).

If serum phosphate is < 1.5 mg/dl (0.48 mmol/l) or creatinine clearance is decreased to < 50 ml/min in any patient receiving emtricitabine and 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 Emtricitabine and tenofovir disoproxil in 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 emtricitabine and tenofovir disoproxil should also be considered in case of progressive decline of renal function when no other cause has been identified.

Use of emtricitabine and tenofovir disoproxil should be avoided with concurrent or recent use of a nephrotoxic medicinal product (see section 4.5). If concomitant use of emtricitabine and 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 emtricitabine/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.

Patients with HIV-1 harbouring mutations
Emtricitabine and tenofovir disoproxil should be avoided in antiretroviral-experienced patients with HIV-1 harbouring the K65R mutation (see section 5.1).

Bone effects

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

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 then appropriate consultation should be obtained.

Patients with HIV and hepatitis B or C virus co-infection
Patients with chronic hepatitis B or C treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions.

Physicians should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV).

In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant Summary of Product Characteristics for these medicinal products.
The safety and efficacy of emtricitabine and tenofovir disoproxil have not been established for the treatment of chronic HBV infection. Emtricitabine and tenofovir individually and in combination have shown activity against HBV in pharmacodynamic studies (see section 5.1). Limited clinical experience suggests that emtricitabine and tenofovir disoproxil have anti-HBV activity when used in antiretroviral combination therapy to control HIV infection.

Discontinuation of emtricitabine and tenofovir disoproxil therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis. Patients co-infected with HIV and HBV who discontinue emtricitabine and tenofovir disoproxil should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. 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.

Use with certain hepatitis C virus antiviral agents
Co-administration of tenofovir disoproxil with ledipasvir/sofosbuvir 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 and a pharmacokinetic enhancer has not been established. The potential risks and benefits associated with co-administration of ledipasvir/sofosbuvir 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 concomitantly with tenofovir disoproxil and a boosted HIV protease inhibitor should be monitored for adverse reactions related to tenofovir disoproxil.

Liver disease
The safety and efficacy of emtricitabine and tenofovir disoproxil have not been established in patients with significant underlying liver disorders. The pharmacokinetics of emtricitabine and tenofovir disoproxil and emtricitabine have not been studied in patients with hepatic impairment. The pharmacokinetics of tenofovir have been studied in patients with hepatic impairment and no dose adjustment is required in these patients. Based on minimal hepatic metabolism and the renal route of elimination for emtricitabine, it is unlikely that a dose adjustment would be required for emtricitabine and tenofovir disoproxil in patients with hepatic impairment (see section 5.2).

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.

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 life style. 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.

HIV infected patients co-infected with hepatitis B virus may experience acute exacerbations of hepatitis associated with immune reactivation syndrome following the initiation of antiretroviral therapy.

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
Emtricitabine and 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 emtricitabine and tenofovir disoproxil.

Ictastan contains lactose monohydrate. Consequently, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interactions

As Ictasan contains emtricitabine and tenofovir disoproxil, any interactions that have been identified with these agents individually may occur with Ictasan. Interaction studies have only been performed in adults.

The steady-state pharmacokinetics of emtricitabine and tenofovir were unaffected when emtricitabine and tenofovir disoproxil were administered together versus each medicinal product dosed alone.

In vitro and clinical pharmacokinetic interaction studies have shown the potential for CYP450 mediated interactions involving emtricitabine and tenofovir disoproxil with other medicinal products is low.

Concomitant use not recommended
Due to similarities with emtricitabine, Ictastan should not be administered concomitantly with other cytidine analogues, such as lamivudine (see section 4.4).

As a fixed combination, Ictastan should not be administered concomitantly with other medicinal products containing any of the components, emtricitabine or tenofovir disoproxil.

Ictastan should not be administered concomitantly with adefovir dipivoxil.

Didanosine: The co-administration of Ictasan and didanosine is not recommended (see section 4.4 and Table 1).

Renally eliminated medicinal products: Since emtricitabine and tenofovir are primarily eliminated by the kidneys, co-administration of emtricitabine and tenofovir disoproxil with medicinal products that reduce renal function or compete for active tubular secretion (e.g. cidofovir) may increase serum concentrations of emtricitabine, tenofovir and/or the co-administered medicinal products.

Use of Ictasan 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).

Other interactions

Interactions between Ictasan or its individual components 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."). If available, 90% confidence intervals are shown in parentheses.

Table 1: Interactions between Ictasan or its individual components and other medicinal products

Medicinal product by therapeutic areas	**Effects on drug levels Mean percent change in AUC, Cmax,Cmin with 90% confidence intervals if available (mechanism)**	**Recommendation concerning co-administration with (emtricitabine 200mg, tenofovir disoproxil 245mg)**
ANTI-INFECTIVES		
Antiretrovirals		
Protease inhibitors		
Atazanavir/Ritonavir/Tenofovir disoproxil (300 mg q.d./100 mg q.d./300 mg q.d.)	Atazanavir: AUC: ↓ 25% (↓ 42 to ↓ 3) Cmax: ↓ 28% (↓ 50 to ↑ 5) Cmin: ↓ 26% (↓ 46 to ↑ 10) Tenofovir: AUC: ↑37% Cmax: ↑ 34% Cmin: ↑ 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).
Atazanavir/Ritonavir/Emtricitabine	Interaction not studied.	
Darunavir/Ritonavir/Tenofovir disoproxil (300 mg q.d./100 mg q.d. /300 mg q.d.)	Darunavir: AUC: ↔ Cmin: ↔ Tenofovir: AUC: ↑ 22% Cmin: ↑ 37%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir associated adverse events, including renal disorders. Renal function should be closely monitored (see section 4.4).

Darunavir/Ritonavir/Emtricitabine	Interaction not studied.	
Lopinavir/Ritonavir/Tenofovir disoproxil (400 mg b.i.d./100 mg b.i.d/300 mg q.d.)	Lopinavir/Ritonavir: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↑ 32% (↑ 25 to ↑ 38) Cmax: ↔ Cmin: ↑ 51% (↑ 37 to ↑ 66)	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/Emtricitabine	Interaction not studied.	
NRTIs		
Didanosine/Tenofovir disoproxil	Co-administration of tenofovir disoproxil and didanosine results in a 40-60% increase in systemic exposure to didanosine.	Co-administration of Emtricitabine/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.
Didanosine/Emtricitabine	Interaction not studied.	

ANTI-INFECTIVES		
Hepatitis C virus (HCV) antiviral agents		
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Atazanavir/Ritonavir (300 mg q.d./100 mg q.d.) + Emtricitabine/Tenofovir isoproxil fumarate (200 mg/300 mg q.d.)[1]	Ledipasvir: AUC: ↑ 96% (↑ 74 to ↑ 121) Cmax: ↑ 68% (↑ 54 to ↑ 84) Cmin: ↑ 118% (↑ 91 to ↑ 150) Sofosbuvir: AUC: ↔ Cmax: ↔ GS-331007[2]: AUC: ↔ Cmax: ↔ Cmin: ↑ 42% (↑ 34 to ↑ 49) Atazanavir: AUC: ↔ Cmax: ↔ Cmin: ↑ 63% (↑ 45 to ↑ 84) Ritonavir: AUC: ↔ Cmax: ↔	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil fumarate, ledipasvir/sofosbuvir and atazanavir/ritonavir may increase adverse reactions related to tenofovir disoproxil fumarate, including renal disorders. The safety of tenofovir disoproxil fumarate when used with ledipasvir/sofosbuvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. The combination should be used

	Cmin: ↑ 45% (↑ 27 to ↑ 64) Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↔ Cmax: ↑ 47% (↑ 37 to ↑ 58) Cmin: ↑ 47% (↑ 38 to ↑ 57)	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 fumarate (200 mg/300 mg q.d.)[1]	Ledipasvir: AUC: ↔ Cmax: ↔ Cmin: ↔ Sofosbuvir: AUC: ↓ 27% (↓ 35 to ↓ 18) Cmax: ↓ 37% (↓ 48 to ↓ 25) GS-331007[2]: AUC: ↔ Cmax: ↔ Cmin: ↔ Darunavir: AUC: ↔ Cmax: ↔ Cmin: ↔ Ritonavir: AUC: ↔ Cmax: ↔ Cmin: ↑ 48% (↑ 34 to ↑ 63) Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↑ 50% (↑ 42 to ↑ 59) Cmax: ↑ 64% (↑ 54 to ↑ 74) Cmin: ↑ 59% (↑ 49 to ↑ 70)	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil fumarate, ledipasvir/sofosbuvir and darunavir/ritonavir may increase adverse reactions related to tenofovir disoproxil fumarate, including renal disorders. The safety of tenofovir disoproxil fumarate 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.) + Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate (600 mg/200 mg/300 mg q.d.)	Ledipasvir: AUC: ↓ 34% (↓ 41 to ↓ 25) Cmax: ↓ 34% (↓ 41 to ↑ 25) Cmin: ↓ 34% (↓ 43 to ↑ 24) Sofosbuvir: AUC: ↔ Cmax: ↔ GS-331007[2]: AUC: ↔ Cmax: ↔ Cmin: ↔ Efavirenz: AUC: ↔ Cmax: ↔ Cmin: ↔ Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↑ 98% (↑ 77 to ↑ 123) Cmax: ↑ 79% (↑ 56 to ↑ 104) Cmin: ↑ 163% (↑ 137 to ↑ 197)	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil fumarate, including renal disorders. Renal function should be closely monitored (see section 4.4).
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Emtricitabine/Rilpivirine/ Tenofovir disoproxil fumarate (200 mg/25 mg/300 mg q.d.)	Ledipasvir: AUC: ↔ Cmax: ↔ Cmin: ↔ Sofosbuvir: AUC: ↔ Cmax: ↔	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir

	GS-331007[2]: AUC: ↔ Cmax: ↔ Cmin: ↔ Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Rilpivirine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↑ 40% (↑ 31 to ↑ 50) Cmax: ↔ Cmin: ↑ 91% (↑ 74 to ↑ 110)	disoproxil fumarate, including renal disorders. Renal function should be closely monitored (see section 4.4).
Sofosbuvir (400 mg q.d.) + Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate (600 mg/200 mg/300 mg q.d.)	Sofosbuvir: AUC: ↔ Cmax: ↓ 19% (↓ 40 to ↑ 10) GS-331007[2]: AUC: ↔ Cmax: ↓ 23% (↓ 30 to ↑ 16) Efavirenz: AUC: ↔ Cmax: ↔ Cmin: ↔ Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↔ Cmax: ↑ 25% (↑ 8 to ↑ 45) Cmin: ↔	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.

Studies conducted withother medicinal products
Emtricitabine: In vitro, emtricitabine did not inhibit metabolism mediated by any of the following human CYP450 isoforms: 1A2, 2A6, 2B6, 2C9, 2C19, 2D6 and 3A4. Emtricitabine did not inhibit the enzyme responsible for glucuronidation. There are no clinically significant pharmacokinetic interactions when emtricitabine is co-administered with indinavir, zidovudine, stavudine or famciclovir.

Tenofovir disoproxil: Co-administration of lamivudine, indinavir, efavirenz, nelfinavir or saquinavir (ritonavir boosted), methadone, ribavirin, rifampicin, adefovir dipivoxil or the hormonal contraceptive norgestimate/ethinyl oestradiol with tenofovir disoproxil did not result in any clinically significant pharmacokinetic interaction.

Emtricitabine and tenofovir disoproxil: Co-administration of tacrolimus with emtricitabine and tenofovir disoproxil did not result in any clinically significant pharmacokinetic interaction.

4.6 Fertility, pregnancy and lactation

Pregnancy
A moderate amount of data on pregnant women (between 300-1,000 pregnancy outcomes) indicate no malformations or foetal/neonatal toxicity associated with emtricitabine and tenofovir disoproxil. Animal studies on emtricitabine and tenofovir disoproxil do not indicate reproductive toxicity (see section 5.3). Therefore the use of Emtricitabine and 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

Emtricitabine and tenofovir have been shown to be excreted in human milk. There is insufficient information on the effects of emtricitabine and tenofovir in newborns/infants. Therefore Ictastan should not be used during breast-feeding.

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

Fertility

No human data on the effect of emtricitabine and tenofovir disoproxil are available. Animal studies do not indicate harmful effects of emtricitabine or 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 both emtricitabine and tenofovir disoproxil.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions considered possibly or probably related to emtricitabine and/or tenofovir disoproxil were nausea (12%) and diarrhoea (7%) in an open- label randomised clinical trial (GS-01-934, see section 5.1). The safety profile of emtricitabine and tenofovir disoproxil in this study was consistent with the previous experience with these agents when each was administered with other antiretroviral agents.

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

Discontinuation of emtricitabine and tenofovir disoproxil therapy in patients co- infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis (see section 4.4).

Tabulated summary of adverse reactions

The adverse reactions considered at least possibly related to treatment with the components of emtricitabine and tenofovir disoproxil from clinical trial and post-marketing experience are listed in Table 2, 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 the individual components of emtricitabine and tenofovir disoproxil based on clinical study and post-marketing experience

Frequency	Emtricitabine	Tenofovir disoproxil
Blood and lymphatic system disorders:		
Common:	neutropenia	
Uncommon:	Anaemia[2]	
Immune system disorders:		
Common:	allergic reaction	
Metabolism and nutrition disorders:		
Very common:		Hypophosphataemia[1]

Common:	hyperglycaemia, hypertriglyceridaemia	
Uncommon:		Hypokalaemia[1]
Rare:		lactic acidosis
Psychiatric disorders:		
Common:	insomnia, abnormal dreams	
Nervous system disorders:		
Very common:	headache	dizziness
Common:	dizziness	headache
Gastrointestinal disorders:		
Very common:	diarrhoea, nausea	diarrhoea, vomiting, nausea
Common:	elevated amylase including elevated pancreatic amylase, elevated serum lipase, vomiting, abdominal pain, dyspepsia	abdominal pain, abdominal distension, flatulence
Uncommon:		pancreatitis
Hepatobiliary disorders:		
Common:	elevated serum aspartate aminotransferase (AST) and/or elevated serum alanine aminotransferase (ALT), hyperbilirubinaemia	increased transaminases
Rare:		hepatic steatosis, hepatitis
Skin and subcutaneous tissue disorders:		
Very common:		rash
Common:	vesiculobullous rash, pustular rash, maculopapular rash, rash, pruritus, urticaria, skin discolouration (increased pigmentation)[2]	
Uncommon:	angioedema[3]	
Rare:		angioedema
Musculoskeletal and connective tissue disorders:		
Very common:	elevated creatine kinase	
Uncommon:		rhabdomyolysis[1], muscular weakness[1]
Rare:		osteomalacia (manifested as bone pain and infrequently contributing to fractures)[1, 3], myopathy[1]

Renal and urinary disorders:		
Uncommon:		increased creatinine, proteinuria proximal renal tubulopathy including Fanconi Syndrome
Rare:		renal failure (acute and chronic), acute tubular necrosis nephritis (including acute interstitial nephritis)[3], nephrogenic diabetes insipidus
General disorders and administration site conditions:		
Very common:		asthenia
Common:	pain, asthenia	

[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]Anaemia was common and skin discolouration (increased pigmentation) was very common when emtricitabine was administered to paediatric patients.
[3]This adverse reaction was identified through post-marketing surveillance but not observed in randomised controlled clinical trials in adults or paediatric HIV clinical trials for emtricitabine or in randomised controlled clinical trials or the tenofovir disoproxil expanded access program for tenofovir disoproxil. The frequency category was estimated from a statistical calculation based on the total number of patients exposed to emtricitabine in randomised controlled clinical trials (n = 1,563) or 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 emtricitabine and tenofovir disoproxil may cause renal damage monitoring of renal function is recommended (see sections 4.4 and 4.8). 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.

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).

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

Other special population(s)
Elderly: Emtricitabine and 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 emtricitabine and 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 any patient with renal impairment treated with emtricitabine and tenofovir disoproxil (see sections 4.2, 4.4 and 5.2).

HIV/HBV orHCV co-infected patients: Only a limited number of patients were co-infected with HBV (n=13) or HCV (n=26) in study GS-01-934. The adverse reaction profile of emtricitabine and tenofovir disoproxil in patients co-infected with HIV/HBV or HIV/HCV was similar to that observed in patients infected with HIV without co-infection. However, as would be expected in this patient population, elevations in AST and ALT occurred more frequently than in the general HIV infected population.

Exacerbations of hepatitis after discontinuation of treatment: In HIV infected patients co-infected with HBV, clinical and laboratory evidence of hepatitis have occurred after discontinuation of treatment (see section 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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 676497; Fax: +353 1 6762517. Website: www.hpra.ie ; E-mail: medsafety@hpra.ie.

4.9 Overdose

If overdose occurs the patient must be monitored for evidence of toxicity (see section 4.8), and standard supportive treatment applied as necessary.

Up to 30% of the emtricitabine dose and approximately 10% of the tenofovir dose can be removed by haemodialysis. It is not known whether emtricitabine or tenofovir can be removed by peritoneal dialysis

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiviral for systemic use; antivirals for treatment of HIV infections, combinations. ATC code: J05AR03.

Mechanism of action and pharmacodynamic effects
Emtricitabine is a nucleoside analogue of cytidine. Tenofovir disoproxil is converted *invivo* to tenofovir, a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate. Both emtricitabine and tenofovir have activity that is specific to human immunodeficiency virus (HIV-1 and HIV-2) and hepatitis B virus.

Emtricitabine and tenofovir are phosphorylated by cellular enzymes to form emtricitabine triphosphate and tenofovir diphosphate, respectively. *In vitro* studies have shown that both emtricitabine and tenofovir can be fully phosphorylated when combined together in cells. Emtricitabine triphosphate and tenofovir diphosphate competitively inhibit HIV-1 reverse transcriptase, resulting in DNA chain termination.

Both emtricitabine triphosphate and tenofovir diphosphate are weak inhibitors of mammalian DNA polymerases and there was no evidence of toxicity to mitochondria *invitro* and *in vivo*.

Antiviral activity in vitro: Synergistic antiviral activity was observed with the combination of emtricitabine and tenofovir *in vitro*. Additive to synergistic effects were observed in combination studies with protease inhibitors, and with nucleoside and non-nucleoside analogue inhibitors of HIV reverse transcriptase.

Resistance: Resistance has been seen *in vitro* and in some HIV-1 infected patients due to the development of the M184V/I mutation with emtricitabine or the K65R mutation with tenofovir. Emtricitabine-resistant viruses with the M184V/I mutation were cross-resistant to lamivudine, but retained sensitivity to didanosine, stavudine, tenofovir and zidovudine. The K65R mutation can also be selected by abacavir or didanosine and results in reduced susceptibility to these agents plus lamivudine, emtricitabine and tenofovir. Tenofovir disoproxil should be avoided in patients with HIV-1 harbouring the K65R mutation. In addition, a K70E substitution in HIV-1 reverse transcriptase has been selected by tenofovir and results in low-level reduced susceptibility to abacavir, emtricitabine, lamivudine and tenofovir.

Patients with HIV-1 expressing three or more thymidine analogue associated mutations (TAMs) that included either the M41L or L210W reverse transcriptase mutation showed reduced susceptibility to tenofovir disoproxil.

In vivo resistance (antiretroviral-naïve patients): In an open-label randomised clinical study (GS-01-934) in antiretroviral-naïve patients, genotyping was performed on plasma HIV-1 isolates from all patients with confirmed HIV RNA > 400 copies/ml at weeks 48, 96 or 144 or at the time of early study drug discontinuation. As of week 144:

The M184V/I mutation developed in 2/19 (10.5%) isolates analysed from patients in the emtricitabine/tenofovir disoproxil /efavirenz group and in 10/29 (34.5%) isolates analysed from the lamivudine/zidovudine/efavirenz group (p-value < 0.05, Fisher's Exact test comparing the emtricitabine+tenofovir disoproxil group to the lamivudine/zidovudine group among all subjects). No virus analysed contained the K65R or K70E mutation. Genotypic resistance to efavirenz, predominantly the K103N mutation, developed in virus from 13/19 (68%) patients in the emtricitabine/tenofovir disoproxil /efavirenz group and in virus from 21/29 (72%) patients in the comparative group.

Clinical efficacy and safety

In an open-label randomised clinical study (GS-01-934), antiretroviral-naïve HIV-1 infected patients received either a once daily regimen of emtricitabine, tenofovir disoproxil and efavirenz (n=255) or a fixed combination of lamivudine and zidovudine (Combivir) administered twice daily and efavirenz once daily (n=254). Patients in the emtricitabine and tenofovir disoproxil group were given emtricitabine/tenofovir disoproxil and efavirenz from week 96 to week 144. At baseline the randomized groups had similar median plasma HIV-1 RNA (5.02 and 5.00 log10 copies/ml) and CD4 counts (233 and 241 cells/ mm^3). The primary efficacy endpoint for this study was the achievement and maintenance of confirmed HIV-1 RNA concentrations < 400 copies/ml over 48 weeks. Secondary efficacy analyses over 144 weeks included the proportion of patients with HIV-1 RNA concentrations < 400 or < 50 copies/ml, and change from baseline in CD4 cell count.

The 48-week primary endpoint data showed that the combination of emtricitabine, tenofovir disoproxil and efavirenz provided superior antiviral efficacy as compared with the fixed combination of lamivudine and zidovudine (Combivir) with efavirenz as shown in Table 3. The 144 week secondary endpoint data are also presented in Table 3.

Table 3: 48-and 144-week efficacy data from study GS-01-934 in which emtricitabine, tenofovir disoproxil and efavirenz were administered to anti retroviral-naïve patients with HIV-1 infection

	GS-01-934 Treatment for 48 weeks			**GS-01-934 Treatment for 144 weeks**		
	Emtricitabine+ tenofovir disoproxil +efavirenz		Lamivudine+ zidovudine +efavirenz	Emtricitabine+ tenofovir disoproxil +efavirenz*		Lamivudine+ Zidovudine +efavirenz
HIV-1 RNA < 400 copies/ml (TLOVR)	84% (206/244)		73% (177/243)	71% (161/227)		58% (133/229)
p-value	0.002**			0.004**		
% difference (95%CI)	11% (4% to 19%)			13% (4% to 22%)		
HIV-1 RNA < 50 copies/ml (TLOVR)	80% (194/244)	70% (171/243)		64% (146/227)	56% (130/231)	
p-value	0.021**			0.082**		
% difference (95%CI)	9% (2% to 17%)			8% (-1% to 17%)		
Mean change from baseline in CD4 cell count (cells/mm^3)	+190	+158		+312	+271	
p-value	0.002[a]			0.089[a]		
Difference (95%CI)	32 (9 to 55)			41 (4 to 79)		

*Patients receiving emtricitabine, tenofovir disoproxil and efavirenz were given emtricitabine and tenofovir disoproxil plus efavirenz from week 96 to 144.

**The p-value based on the Cochran-Mantel-Haenszel Test stratified for baseline CD4 cell count TLOVR=Time to Loss of Virologic Response
a: Van Elteren Test

In a separate randomised clinical study (M02-418), one hundred and ninety antiretroviral-naïve adults were also treated once daily with emtricitabine and tenofovir disoproxil in combination with lopinavir/ritonavir given once or twice daily. At 48 weeks, 70% and 64% of patients demonstrated HIV-1 RNA < 50 copies/ml with the once and twice daily regimens of lopinavir/ritonavir, respectively. The mean changes in CD4 cell count from baseline were +185cells/mm^3 and +196 cells/ mm^3 with the once and twice daily regimens of lopinavir/ritonavir, respectively.

Limited clinical experience in patients co-infected with HIV and HBV suggests that treatment with emtricitabine or tenofovir disoproxil in antiretroviral combination therapy to control HIV infection also results in a reduction in HBV DNA (3 log10 reduction or 4 to 5 log10 reduction, respectively) (see section 4.4).

Paediatric population
The safety and efficacy of emtricitabine and tenofovir disoproxil in children under the age of 18 years have not been established.

5.2 Pharmacokinetic properties

Absorption
The bioequivalence of one emtricitabine and tenofovir disoproxil film-coated tablet with one emtricitabine 200 mg hard capsule and one tenofovir disoproxil 245 mg film-coated tablet was established following single dose administration to fasting healthy subjects. Following oral administration of emtricitabine and tenofovir disoproxil to healthy subjects, emtricitabine and tenofovir disoproxil are rapidly absorbed and tenofovir disoproxil is converted to tenofovir. Maximum emtricitabine and tenofovir concentrations are observed in serum within 0.5 to 3.0 h of dosing in the fasted state. Administration of emtricitabine and tenofovir disoproxil with food resulted in a delay of approximately three quarters of an hour in reaching maximum tenofovir concentrations and increases in tenofovir AUC and Cmax of approximately 35% and 15%, respectively, when administered with a high fat or light meal, compared to administration in the fasted state. In order to optimise the absorption of tenofovir, it is recommended that emtricitabine and tenofovir disoproxil should be taken with food.

Distribution
Following intravenous administration the volume of distribution of emtricitabine and tenofovir was approximately 1.4 l/kg and 800 ml/kg, respectively. After oral administration of emtricitabine or tenofovir disoproxil, emtricitabine and tenofovir are widely distributed throughout the body. *In vitro* binding of emtricitabine to human plasma proteins was < 4% and independent of concentration over the range of 0.02 to 200 µg/ml. *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
There is limited metabolism of emtricitabine. The biotransformation of emtricitabine includes oxidation of the thiol moiety to form the 3'-sulphoxide diastereomers (approximately 9% of dose) and conjugation with glucuronic acid to form 2'-O-glucuronide (approximately 4% of dose). *Invitro* studies have determined that neither tenofovir disoproxil nor tenofovir are substrates for the CYP450 enzymes. Neither emtricitabine nor tenofovir inhibited *invitro* drug metabolism mediated by any of the major human CYP450 isoforms involved in drug biotransformation. Also, emtricitabine did not inhibit uridine-5'-diphosphoglucuronyl transferase, the enzyme responsible for glucuronidation.

Elimination
Emtricitabine is primarily excreted by the kidneys with complete recovery of the dose achieved in urine (approximately 86%) and faeces (approximately 14%). Thirteen percent of the emtricitabine dose was recovered in urine as three metabolites. The systemic clearance of emtricitabine averaged 307 ml/min. Following oral administration, the elimination half-life of emtricitabine is approximately 10 hours.

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. The apparent clearance of tenofovir averaged approximately 307 ml/min. Renal clearance has been estimated to be 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 elimination half-life of tenofovir is approximately 12 to18 hours.

Elderly
Pharmacokinetic studies have not been performed with emtricitabine or tenofovir in the elderly (over 65 years of age).

Gender
Emtricitabine and tenofovir pharmacokinetics are similar in male and female patients.

Ethnicity
No clinically important pharmacokinetic difference due to ethnicity has been identified for emtricitabine. The pharmacokinetics of tenofovir have not been specifically studied in different ethnic groups.

Paediatric population
In general, the pharmacokinetics of emtricitabine in infants, children and adolescents (aged 4 months up to 18 years) are similar to those seen in adults. Pharmacokinetic studies have not been performed with tenofovir in children and adolescents (under 18 years of age).

Renal impairment
Limited pharmacokinetic data are available for emtricitabine and tenofovir after co-administration of separate preparations or as emtricitabine and tenofovir disoproxil in patients with renal impairment. Pharmacokinetic parameters were mainly determined following administration of single doses of emtricitabine 200 mg or tenofovir disoproxil 245 mg to non-HIV infected patients with varying degrees of renal impairment. The degree of renal impairment was defined according to baseline creatinine clearance (CrCl) (normal renal function when CrCl > 80 ml/min; mild impairment with CrCl = 50-79 ml/min; moderate impairment with CrCl = 30-49 ml/min and severe impairment with CrCl = 10-29 ml/min).

The mean (%CV) emtricitabine drug exposure increased from 12 (25%) µg•h/ml in subjects with normal renal function, to 20 (6%) µg•h/ml, 25 (23%) µg•h/ml and 34 (6%) µg•h/ml, in patients with mild, moderate and severe renal impairment, respectively.

The mean (%CV) tenofovir drug exposure increased from 2,185 (12%) ng•h/ml in patients with normal renal function, to 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, respectively.

The increased dose interval for emtricitabine and tenofovir disoproxil in patients with moderate renal impairment is expected to result in higher peak plasma concentrations and lower Cmin levels as compared to patients with normal renal function. The clinical implications of this are unknown.

In patients with end-stage renal disease (ESRD) requiring haemodialysis, between dialysis drug exposures substantially increased over 72 hours to 53 (19%) µg•h/ml of emtricitabine, and over 48 hours to 42,857 (29%) ng•h/ml of tenofovir.

It is recommended that the dosing interval for emtricitabine and tenofovir disoproxil is modified in patients with creatinine clearance between 30 and 49 ml/min. Emtricitabine and tenofovir disoproxil is not suitable for patients with CrCl < 30 ml/min or for those on haemodialysis (see section 4.2).

A small clinical study was conducted to evaluate the safety, antiviral activity and pharmacokinetics of tenofovir disoproxil in combination with emtricitabine in HIV infected patients with renal impairment. A subgroup of patients with baseline creatinine clearance between 50 and 60 ml/min, receiving once daily dosing, had a 2-4-fold increase in tenofovir exposure and worsening renal function.

Hepatic impairment
The pharmacokinetics of emtricitabine and tenofovir disoproxil have not been studied in patients with hepatic impairment. However, it is unlikely that a dose adjustment would be required for emtricitabine and tenofovir disoproxil in patients with hepatic impairment.

The pharmacokinetics of emtricitabine have not been studied in non-HBV infected subjects with varying degrees of hepatic insufficiency. In general, emtricitabine pharmacokinetics in HBV infected subjects were similar to those in healthy subjects and in HIV infected subjects.

A single 245 mg dose of tenofovir disoproxil was administered to non-HIV infected patients with varying degrees of hepatic impairment defined according to Child-Pugh-Turcotte (CPT) classification. Tenofovir pharmacokinetics were not substantially altered in subjects with hepatic impairment suggesting that no dose adjustment is required in these subjects. The mean (%CV)

tenofovir Cmax and AUC0-∞ values were 223 (34.8%) ng/ml and 2,050 (50.8%) ng•h/ml, respectively, in normal subjects compared with 289 (46.0%) ng/ml and 2,310 (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.

5.3 Preclinical safety data

Emtricitabine: Non-clinical data on emtricitabine reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development.

Tenofovir disoproxil: Non-clinical safety pharmacology studies on tenofovir disoproxil reveal no special hazard for humans. 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 toxicity 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.

Combination of emtricitabine and tenofovir disoproxil: Genotoxicity and repeated dose toxicity studies of one month or less with the combination of these two components found no exacerbation of toxicological effects compared to studies with the separate components.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tabletcore:
Lactose monohydrate
Microcrystalline cellulose (E460)
Starch, Pregelatinised (Maize)
Croscarmellose sodium
Magnesium stearate (E470b)

Film-coating:
Poly(Vinyl Alcohol) (E1203)
Titanium Dioxide (E171)
Macrogol 3350 (E1521)
Talc (E553b)
Indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years. After 1st opening: 30 days when stored under 25 °C

6.4 Special precautions for storage

Store in the original package in order to protect from moisture. Keep the container tightly closed.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle with a polypropylene child-resistant cap containing 30 film-coated tablets and an HDPE canister containing desiccant silica gel, freely inside the bottle.

Outer cartons containing 30 (1 x 30) film-coated tablet and 90 (3 x30) film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Ireland Ltd.
Euro House
Euro Business Park
Little Island
Cork T45 K857
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2315/153/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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