1. Name of the medicinal product

INN Name **:** Emtricitabine and Tenofovir Disoproxil Fumarate Tablets 200mg/300mg

Propriority Name **:** Emtricitabine and Tenofovir Disoproxil Fumarate Tablets 200mg/300mg

Strength : 200mg/300 mg

Pharmaceutical form: film coated Tablet

2. Qualitative and quantitative composition

200 mg of Emtricitabine and 300 mg of Tenofovir Disoproxil Fumarate equivalent to 245 mg of Tenofovir Disoproxil.

For excipients, see 6.1.

3. Pharmaceutical form

Dosage form: Tablet

Description: Description: Blue, Capsule shaped, film coated tablets, debossed with 'H' on one side and '124' on the other side.

4. Clinical particulars

4.1 Therapeutic indications

It is a fixed dose combination of emtricitabine and tenofovir disoproxil fumarate. It is indicated in antiretroviral combination therapy for the treatment of HIV 1 infected adults..

4.2 Posology and method of administration

Posology

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

Adults: The recommended dose of Emtricitabine and Tenofovir Disoproxil Fumarate Tablets 200/300 mg is one tablet, taken orally, once daily. In order to optimise the absorption of tenofovir, it is recommended that Emtricitabine and Tenofovir Disoproxil Fumarate Tablets 200/300 mg should be taken with food. Even a light meal improves absorption of tenofovir from the combination tablet.

Where discontinuation of therapy with one of the components of Emtricitabine and Tenofovir Disoproxil Fumarate Tablets 200/300 mg is indicated or where dose modification is necessary,

separate preparations of emtricitabine and tenofovir disoproxil fumarate are available. Please refer to the Summary of Product Characteristics for these medicinal products.

Children and adolescents: Emtricitabine and Tenofovir Disoproxil Fumarate Tablets 200/300 mg is not recommended for use in children below the age of 18 years due to insufficient data on safety and efficacy.

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 Fumarate Tablets 200/300 mg 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 Fumarate Tablets 200/300 mg 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.

Mild renal impairment (creatinine clearance 50- 80 ml/min): Limited data from clinical studies support once daily dosing of Emtricitabine and Tenofovir Disoproxil Fumarate Tablets 200/300 mg in patients with mild renal impairment.

Moderate renal impairment (creatinine clearance 30 49 ml/min): Administration of Emtricitabine and Tenofovir Disoproxil Fumarate Tablets 200/300 mg every 48 hours is recommended, based on modelling of single-dose pharmacokinetic data for emtricitabine and tenofovir disoproxil fumarate in non- HIV infected subjects with varying degrees of renal impairment.

Severe renal impairment (creatinine clearance < 30 ml/min) and haemodialysis patients: Emtricitabine and Tenofovir Disoproxil Fumarate Tablets 200/300 mg 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 Fumarate Tablets 200/300 mg 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 fumarate 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 Fumarate Tablets 200/300 mg in patients with hepatic impairment.

If Emtricitabine and Tenofovir Disoproxil Fumarate Tablets 200/300 mg is discontinued in patients co-infected with HIV and HBV, these patients should be closely monitored for evidence of exacerbation of hepatitis.

4.3 Contraindications

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

4.4 Special warnings and special precautions for use

Emtricitabine and Tenofovir Disoproxil Fumarate Tablets 200/300 mg should not be administered concomitantly with other medicinal products containing emtricitabine, tenofovir disoproxil (as fumarate) or other cytidine analogues, such as lamivudine and zalcitabine.

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 fumarate 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 Fumarate Tablets 200/300 mg is administered with a third nucleoside analogue

Patients receiving Emtricitabine and Tenofovir Disoproxil Fumarate Tablets 200/300 mg 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.

Patients must be advised that antiretroviral therapies, including Emtricitabine and Tenofovir Disoproxil Fumarate Tablets 200/300 mg, have not been proven to prevent the risk of transmission of HIV to others through sexual contact or contamination with blood. Appropriate precautions must continue to be used.

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 fumarate in clinical practice.

It is recommended that creatinine clearance is calculated in all patients prior to initiating therapy with Emtricitabine and Tenofovir Disoproxil Fumarate Tablets 200/300 mg and renal function (creatinine clearance and serum phosphate) is also monitored every four weeks during the first year and then every three months. In patients at risk for renal impairment, including patients who have previously experienced renal events while receiving adefovir dipivoxil, consideration should be given to more frequent monitoring of renal function.

Patients with renal impairment (creatinine clearance < 80 ml/min), including haemodialysis patients: Renal safety with Emtricitabine and Tenofovir Disoproxil Fumarate Tablets 200/300 mg 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. 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 fumarate in combination with emtricitabine every 24 hours had a 2 4 fold higher exposure to tenofovir and worsening of renal function. Therefore, a careful benefit-risk assessment is needed when Emtricitabine and Tenofovir Disoproxil Fumarate Tablets 200/300 mg 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 Fumarate Tablets 200/300 mg at a prolonged dosing interval. The use of Emtricitabine and Tenofovir Disoproxil Fumarate Tablets 200/300 mg 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.

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 Fumarate Tablets 200/300 mg, renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations. Consideration should also be given to interrupting treatment with Emtricitabine and Tenofovir Disoproxil Fumarate Tablets 200/300 mg in patients with creatinine clearance decreased to < 50 ml/min or decreases in serum phosphate to < 1.0 mg/dl (0.32 mmol/l).

Use of Emtricitabine and Tenofovir Disoproxil Fumarate Tablets 200/300 mg should be avoided with concurrent or recent use of a nephrotoxic medicinal product.

Emtricitabine and Tenofovir Disoproxil Fumarate Tablets 200/300 mg should be avoided in antiretroviral experienced patients with HIV 1 harbouring the K65R mutation.

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

Bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy. 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 Fumarate Tablets 200/300 mg 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. Limited clinical experience suggests that emtricitabine and tenofovir disoproxil fumarate have anti HBV activity when used in antiretroviral combination therapy to control HIV infection

Discontinuation of Emtricitabine and Tenofovir Disoproxil Fumarate Tablets 200/300 mg 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 Fumarate Tablets 200/300 mg 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.

Liver disease: The safety and efficacy of Emtricitabine and Tenofovir Disoproxil Fumarate Tablets 200/300 mg have not been established in patients with significant underlying liver disorders. The pharmacokinetics of Emtricitabine and Tenofovir Disoproxil Fumarate Tablets 200/300 mg 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 Fumarate Tablets 200/300 mg in patients with hepatic impairment.

Patients with pre existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Lipodystrophy: Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors and lipoatrophy and nucleoside reverse transcriptase inhibitors has been hypothesised. A higher risk of lipodystrophy has been associated with

individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

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

Mitochondrial dysfunction: Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV negative infants exposed in utero and/or postnatally to nucleoside analogues. The main adverse reactions reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactataemia, hyperlipasaemia). These events are often transitory. Some late onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether the neurological disorders are transient or permanent is currently unknown. Any child exposed *in utero* to nucleoside and nucleotide analogues, even HIV negative children, should have clinical and laboratory follow up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

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

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 combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Co administration of tenofovir disoproxil fumarate and didanosine: is not recommended. Co administration of tenofovir disoproxil fumarate and didanosine results in a 40-60% increase in systemic exposure to didanosine that may increase the risk of didanosine-related adverse reactions. Rare cases of pancreatitis and lactic acidosis, sometimes fatal, have been reported. Co administration of Tenofovir disoproxil fumarate and didanosine at a dose of 400 mg daily has been associated with a significant decrease in CD4 cell count, possibly due to an intracellular interaction increasing phosphorylated (i.e. active) didanosine. A decreased dosage of 250 mg didanosine co administered with tenofovir disoproxil fumarate therapy has been associated with reports of high rates of virological failure within several tested combinations.

Emtricitabine and Tenofovir Disoproxil Fumarate Tablets 200/300 mg 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 interaction

Interaction studies have only been performed in adults

The likelihood of metabolic interactions is low due to limited metabolism and plasma protein binding and almost complete renal clearance.

Administration of trimethoprim/sulfamethoxazole 160 mg/800 mg results in a 40 % increase in lamivudine exposure, because of the trimethoprim component; the sulfamethoxazole component did not interact. However, unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary. Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole. When concomitant administration is warranted, patients should be monitored clinically. Co-administration of lamivudine with high doses of co-trimoxazole for the treatment of Pneumocystis carinii pneumonia (PCP) and toxoplasmosis should be avoided.

The possibility of interactions with other medicinal products administered concurrently should be considered, particularly when the main route of elimination is active renal secretion via the organic cationic transport system e.g. trimethoprim. Other medicinal products (e.g. ranitidine, cimetidine) are eliminated only in part by this mechanism and were shown not to interact with

lamivudine. The nucleoside analogues (e.g. didanosine) like zidovudine , are not eliminated by this mechanism and are unlikely to interact with lamivudine.

A modest increase in Cmax (28 %) was observed for zidovudine when administered with lamivudine, however overall exposure (AUC) is not significantly altered. Zidovudine has no effect on the pharmacokinetics of lamivudine.

Lamivudine metabolism does not involve CYP3A, making interactions with medicinal products metabolized by this system (e.g. PIs) unlikely.

4.6 Pregnancy and lactation

Pregnancy:

For emtricitabine and tenofovir disoproxil fumarate, insufficient data on exposed pregnancies are available.

Animal studies do not indicate direct or indirect harmful effects of emtricitabine or tenofovir disoproxil fumarate with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.

However, Emtricitabine and Tenofovir Disoproxil Fumarate Tablets 200/300 mg should not be used during pregnancy unless no other alternative is available.

The use of Emtricitabine and Tenofovir Disoproxil Fumarate Tablets 200/300 mg must be accompanied by the use of effective contraception.

Lactation:

It is not known whether emtricitabine or tenofovir are excreted in human milk.

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.

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 fumarate.

4.8 Undesirable effects

In an open-label randomised clinical study in antiretroviral-naïve patients, patients received emtricitabine, tenofovir disoproxil fumarate and efavirenz for 144 weeks (administered as the combination formulation Emtricitabine and Tenofovir Disoproxil Fumarate Tablets 200/300 mg, plus efavirenz from week 96). The safety profile of emtricitabine and tenofovir disoproxil fumarate was consistent with the previous experience with these agents when each was

administered with other antiretroviral agents. The most frequently reported adverse reactions considered possibly or probably related to emtricitabine and/or tenofovir disoproxil fumarate were nausea (12%) and diarrhoea (7%).

The adverse reactions considered at least possibly related to treatment with the components of Emtricitabine and Tenofovir Disoproxil Fumarate Tablets 200/300 mg from clinical trial and post marketing experience are listed below by body system organ class and absolute frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (1/10), common (1/100 to < 1/10), uncommon (1/1,000 to < 1/100), rare (1/10,000 to < 1/1,000), very rare (< 1/10,000) or not known (identified through post-marketing safety surveillance and the frequency cannot be estimated from the available data).

Blood and lymphatic system disorders:

Common: neutropenia

Uncommon: anaemia

Immune system disorders:

Common: allergic reaction

Metabolism and nutrition disorders:

Very common: hypophosphataemia

Common: hyperglycaemia, hypertriglyceridaemia

Rare: lactic acidosis

Not known: hypokalaemia

Lactic acidosis, usually associated with hepatic steatosis, has been reported with the use of nucleoside analogues.

Psychiatric disorders:

Common: insomnia, abnormal dreams

Nervous system disorders:

Very common: headache, dizziness

Respiratory, thoracic and mediastinal disorders:

Very rare: dyspnoea

Gastrointestinal disorders:

Very common: diarrhoea, vomiting, nausea

Common: elevated serum lipase, elevated amylase including elevated pancreatic amylase, abdominal pain, dyspepsia, flatulence

Rare: pancreatitis

Hepatobiliary disorders:

Common: increased transaminases, hyperbilirubinaemia

Very rare: hepatitis

Not known: hepatic steatosis

Skin and subcutaneous tissue disorders:

Common: urticaria, vesiculobullous rash, pustular rash, maculopapular rash, pruritus, rash and skin discolouration (increased pigmentation)

Musculoskeletal and connective tissue disorders:

Very common: elevated creatine kinase

Not known: rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), muscular weakness, myopathy

Renal and urinary disorders:

Rare: renal failure (acute and chronic), proximal renal tubulopathy including Fanconi syndrome, increased creatinine, proteinuria

Very rare: acute tubular necrosis

Not known: nephritis (including acute interstitial nephritis), nephrogenic diabetes insipidus.

General disorders and administration site conditions:

Common: pain, asthenia

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), hypokalaemia, muscular weakness, myopathy and hypophosphataemia. These events are not considered to be causally associated with tenofovir disoproxil fumarate therapy in the absence of proximal renal tubulopathy.

In addition anaemia was common and skin discolouration (increased pigmentation) was very common when emtricitabine was administered to paediatric patients.

HIV/HBV or HCV 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 fumarate 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.

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

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

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

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

4.9 Overdose

If overdose occurs the patient must be monitored for evidence of toxicity, 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 fumarate is converted *in vivo* 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 *in vitro* 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. No other pathways of resistance to emtricitabine or tenofovir have been identified. Emtricitabine resistant viruses with the M184V/I mutation were cross resistant to lamivudine, but retained sensitivity to didanosine, stavudine, tenofovir, zalcitabine and zidovudine. The K65R mutation can also be selected by abacavir, didanosine or zalcitabine and results in reduced susceptibility to these agents plus lamivudine,emtricitabine and tenofovir. Tenofovir disoproxil fumarate should be avoided in patients with HIV- 1 harbouring the K65R mutation.

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 fumarate.

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 fumarate/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 fumarate group to the lamivudine/zidovudine group among all subjects).

• No virus analysed contained the K65R mutation.

• Genotypic resistance to efavirenz, predominantly the K103N mutation, developed in virus from 13/19 (68%) patients in the emtricitabine/tenofovir disoproxil fumarate/efavirenz group and in virus from 21/29 (72%) patients in the comparative group.

Clinical experience: 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 fumarate 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 fumarate group were given Emtricitabine and Tenofovir Disoproxil Fumarate Tablets 200/300mg and efavirenz from week 96 to week 144. At baseline the randomised groups had similar median plasma HIV 1 RNA (5.02 and 5.00 log10 copies/ml) and CD4 counts (233 and 241 cells/mm3). 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 fumarate and efavirenz provided superior antiviral efficacy as compared with the fixed combination of lamivudine and zidovudine (Combivir) with efavirenz as shown in the below Table . The 144 week secondary endpoint data are also presented in the below Table .

Table : 48 and 144 week efficacy data from study GS 01 934 in which emtricitabine, Tenofovir disoproxil fumarate and efavirenz were administered to antiretroviral naïve patients with HIV 1 infection.

	GS 01 934 Treatment for 48 weeks		**GS 01 934 Treatment for 144 weeks**	
	Emtricitabine+ tenofovir disoproxil fumarate+efavirenz	Lamivudine+zidovu dine+ efa-virenz	Emtricitabine+ Tenofovir disoproxil fumarate+efavirenz*	Lamivudine+ zidovudine+efaviren z
HIV 1RNA < 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 inCD4 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 fumarate and efavirenz were given Emtricitabine and Tenofovir Disoproxil Fumarate Tablets 200/300 mg 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 fumarate 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 +185 cells/mm3 and +196 cells/mm3 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 fumarate 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).

5.2 Pharmacokinetic properties

Absorption: The bioequivalence of one Emtricitabine and Tenofovir Disoproxil Fumarate Tablets 200/300 mg film coated tablet with one emtricitabine 200 mg hard capsule and one tenofovir disoproxil fumarate 245 mg film coated tablet was established following single dose administration to fasting healthy subjects. Following oral administration of Emtricitabine and Tenofovir Disoproxil Fumarate Tablets 200/300 mg to healthy subjects, emtricitabine and tenofovir disoproxil fumarate are rapidly absorbed and tenofovir disoproxil fumarate 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 Fumarate Tablets 200/300 mg 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 Fumarate Tablets 200/300 mg 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 fumarate, 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). *In vitro* studies have determined that neither tenofovir disoproxil fumarate nor tenofovir are substrates for the CYP450 enzymes. Neither emtricitabine nor tenofovir inhibited *in vitro* 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 to 18 hours.

Age, gender and ethnicity: Emtricitabine and tenofovir pharmacokinetics are similar in male and female patients. 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). Pharmacokinetic studies have not been performed with emtricitabine or tenofovir in the elderly (over 65 years).

Renal impairment: Limited pharmacokinetic data are available for emtricitabine and tenofovir after coadministration of separate preparations or as Emtricitabine and Tenofovir Disoproxil Fumarate Tablets 200/300 mg 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 Fumarate Tablets 200/300 mg 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 Fumarate Tablets 200/300 mg is modified in patients with creatinine clearance between 30 and 49 ml/min. Emtricitabine and Tenofovir Disoproxil Fumarate Tablets 200/300 mg is not suitable for patients with CrCl < 30 ml/min or for those on haemodialysis.

A small clinical study was conducted to evaluate the safety, antiviral activity and pharmacokinetics of tenofovir disoproxil fumarate 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 Fumarate Tablets 200/300 mg 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 Fumarate Tablets 200/300 mg 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

Non clinical data on emtricitabine reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity. Emtricitabine did not show any carcinogenic potential in long term oral carcinogenicity studies in mice and rats.

Preclinical studies of tenofovir disoproxil fumarate conducted in rats, dogs and monkeys revealed target organ effects in gastrointestinal tract, kidney, bone and a decrease in serum phosphate concentration. Bone toxicity was diagnosed as osteomalacia (monkeys) and reduced bone mineral density (rats and dogs). Findings in the rat and monkey studies indicated that there was a substance related decrease in intestinal absorption of phosphate with potential secondary reduction in bone mineral density. The mechanisms of these toxicities are not completely understood.

Conventional reproductive/developmental toxicity studies with emtricitabine and tenofovir disoproxil fumarate reveal no special hazard for humans.

Tenofovir disoproxil fumarate was positive in two out of three *in vitro* genotoxicity studies but negative in the *in vivo* micronucleus assay.

Tenofovir disoproxil fumarate did not show any carcinogenic potential in a long term oral carcinogenicity study in rats. A long term oral carcinogenicity study in mice showed a low incidence of duodenal tumours, considered likely related to high local concentrations in the gastrointestinal tract at a dose of 600 mg/kg/day. While the mechanism of tumour formation is uncertain, the findings are unlikely to be of relevance to humans.

The combination of emtricitabine and tenofovir disoproxil fumarate was positive in the *in vitro* mouse lymphoma assay, with comparable results to those obtained for tenofovir disoproxil fumarate alone. The combination of emtricitabine and tenofovir disoproxil fumarate was negative in the bacterial reverse mutation assay (Ames assay).

A one month dog study using the combination of emtricitabine and tenofovir disoproxil fumarate, found no exacerbation of toxicological effects compared to the separate components.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablets contents: Pregelatinized Starch, Lactose Monohydrate, microcrystalline Cellulose (Avicel PH 102), Croscarmellose Sodium, Purified water, Magnesium Stearate, Opadry II Blue 32K10849.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C and protect from moisture.

6.5 Nature and contents of container

HDPE container pack of 30's count

6.6 Special precautions for disposal and other handling

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

7. Marketing Authorisation Holder and Manufacturing Site Addresses

Marketing authorization Holder:

Name: **Hetero Labs Limited**

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8. Marketing authorization number

9. Date of first registration/renewal of the registration

10. Date of revision of the text