

## **1. NAME OF THE MEDICINAL PRODUCT**

Emtricitabine/Tenofovir Disoproxil Fumarate film coated tablets 200 mg/300 mg

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each film coated tablet contains  
Emtricitabine 200 mg  
Tenofovir Disoproxil Fumarate 300 mg

### **Excipient(s) with known effect:**

Each film coated tablet contains 136.00 mg of Lactose monohydrate

For a full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Film coated tablet.

Blue coloured, oval shaped, film coated tablets debossed with "M117" on one side and plain on other side.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications:**

Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets is indicated in combination with at least one other antiretroviral product for the treatment of HIV-1 infection in adults and adolescents over 10 years of age and weighing at least 30 kg.

Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets may be used for pre-exposure prophylaxis (PrEP) in as an additional prevention choice for adults and adolescents (weighing at least 35 kg) at substantial risk of HIV infection as part of combination prevention approaches.

Consideration should be given to official guidelines for prevention and treatment of HIV-1 infection (e.g. those of the WHO).

### **4.2 Posology and method of administration**

Therapy should be initiated by a health care provider experienced in the prevention and management of HIV infection.

#### ***Posology***

##### **Adults and adolescents**

The recommended dose of Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets is one tablet (200 mg emtricitabine and 300 mg tenofovir disoproxil fumarate ), taken orally, once daily without regard to food.

### **Special populations**

#### *Children and adolescents*

HIV-therapy: Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets should not be used in children under 10 years of age and in adolescents weighing less than 30 kg since appropriate dose adjustments cannot be achieved with this product (see section 5.2).

PrEP: Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets should not be used in children under 10 years of age and in adolescents weighing less than 35 kg due to insufficient data on safety and efficacy (see section 5.2).

#### *Elderly*

There is no need for dose adjustment of Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets in the elderly, except if there is evidence of renal impairment (see sections 4.4 and 5.2).

#### *Renal impairment*

Emtricitabine and tenofovir are both eliminated by renal excretion. Thus, exposure to both compounds increases in patients with renal dysfunction. The long term safety of tenofovir and emtricitabine in mild renal impairment (creatinine clearance 50-80 ml/min) has not been fully assessed. Therefore, in patients with renal impairment Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets 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 such patients (see sections 4.4 and 5.2).

*Mild renal impairment (creatinine clearance 50-80 ml/min):* Limited data from clinical studies support once daily dosing of Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets in patients with mild renal impairment (see section 4.4).

*Moderate renal impairment (creatinine clearance 30-49 ml/min):* Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets should not be used for PrEP in HIV-1 uninfected individuals with estimated creatinine clearance below 60 ml/min

For HIV-therapy administration of Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets 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 (see section 4.4).

*Severe renal impairment (creatinine clearance < 30 ml/min) and haemodialysis patients:* Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets is not recommended for patients with severe renal impairment (creatinine clearance < 30 ml/min) and in patients who

require haemodialysis because appropriate reductions cannot be achieved with the combination tablet.

#### *Hepatic impairment*

The pharmacokinetics of tenofovir has been studied in patients with hepatic impairment. No dose adjustment is required for tenofovir disoproxil fumarate in these patients. The pharmacokinetics of emtricitabine has not been studied in patients with hepatic impairment. 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/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets in patients with hepatic impairment (see sections 4.4 and 5.2).

#### *Discontinuation of therapy*

Where discontinuation of therapy of HIV-1 infection with one of the components of Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets is indicated or where dose modification is necessary, separate preparations of emtricitabine and tenofovir disoproxil fumarate should be used.

If Emtricitabine/Tenofovir Disoproxil Fumarate 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).

Individuals who wish to discontinue oral PrEP should be advised to continue PrEP dosing for at least 4 weeks after the last potential HIV exposure.

#### *Advice on missed dose*

If a dose of Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets is missed within 12 hours of the time it is usually taken, the individual should take the medicine as soon as possible and resume the normal dosing schedule. If a dose of Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets is missed by more than 12 hours and it is almost time for the next dose, the individual should not take the missed dose and simply resume the usual dosing schedule.

If the individual vomits within 1 hour of taking Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets, another tablet should be taken. If vomiting occurs more than 1 hour after taking the dose, the individual does not need to take an extra dose and can take the next dose as usual when it is due.

#### ***Method of administration***

Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets should be swallowed whole. Alternatively, the tablets may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately.

### **4.3 Contraindications**

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

### **4.4 Special warnings and special precautions for use**

## ***General***

HBV antibody testing should be offered to all individuals before initiating therapy with Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets (see below *Co-infection with HIV-1 and hepatitis B*).

## ***Pre-exposure prophylaxis***

### **Comprehensive Management to Reduce the Risk of Acquiring HIV-1:**

Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets should be used for pre-exposure prophylaxis only as part of a comprehensive prevention strategy that includes other prevention measures, such as safer sex practices, because it is not always effective in preventing the acquisition of HIV-1 [See Pharmacodynamic properties (Section 5.1)].

Uninfected individuals should be counselled about safer sex practices that include consistent and correct use of condoms, knowledge of their HIV-1 status and that of their partner(s), and regular testing for other sexually transmitted infections that can facilitate HIV-1 transmission (such as syphilis and gonorrhoea).

Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets should be used to reduce the risk of acquiring HIV-1 only in individuals who are confirmed to be HIV-negative. HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking only Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets, because alone it does not constitute a complete treatment regimen for HIV-1. Therefore, care should be taken to minimize drug exposure in HIV-infected individuals.

Many HIV-1 tests, such as rapid tests, detect anti-HIV antibodies and may not identify HIV-1 during the acute stage of infection. Prior to initiating Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets for a PrEP indication, seronegative individuals should be evaluated for current or recent signs or symptoms consistent with acute viral infections (e.g., fever, fatigue, myalgia, skin rash, etc.) and asked about potential exposure events (e.g., unprotected, or condom broke during sex with an HIV-1 infected partner) that may have occurred within the last month.

If clinical symptoms consistent with acute viral infection are present and recent (<1 month) exposures are suspected, starting PrEP should be delayed for at least one month. HIV-1 status should be then reconfirmed using a reliable test as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection.

While using emtricitabine/tenofovir DF for PrEP, HIV-1 screening tests should be repeated at least every 3 months. If symptoms consistent with acute HIV-1 infection develop following a potential exposure event, PrEP should be discontinued until negative infection status is confirmed using a reliable test as an aid in the diagnosis of HIV-1, including acute or primary HIV-1 infection.

Uninfected individuals should be counselled to strictly adhere to the recommended Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets dosing schedule. The effectiveness of emtricitabine/tenofovir DF in reducing the risk of acquiring HIV-1 is strongly correlated with adherence as demonstrated by measurable drug levels in clinical trials.

An assessment of the risk for HIV-1 acquisition should be done at each visit.

Preliminary data indicate that the time elapsing before oral PrEP is fully effective is five to seven days for anal sex and up to three weeks for vaginal sex. Individuals who wish to discontinue oral PrEP should be advised to continue PrEP dosing for at least 4 weeks after the last potential HIV exposure.

### ***HIV-therapy***

Patients using Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets should be advised that antiretroviral therapy has not been proven to prevent fully the risk of transmission of HIV to others through sexual contact or contamination with blood. Appropriate precautions must continue to be taken.

### ***Co-administration of other medicinal product***

Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets should not be administered concomitantly with other medicinal products containing emtricitabine, tenofovir disoproxil (as fumarate), tenofovir alafenamide or other cytidine analogues, such as lamivudine (see below and section 4.5). Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets should not be administered concomitantly with adefovir dipivoxil.

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. Lamivudine and emtricitabine are similar in structure, pharmacokinetics and pharmacodynamics. Therefore, the same problems may be seen if Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets is administered with a third nucleoside analogue.

Co-administration of tenofovir disoproxil fumarate and didanosine is not recommended. This co-administration may increase the risk of didanosine-related adverse events. Rare cases of pancreatitis and lactic acidosis, sometimes fatal, have been reported. Co-administration of tenofovir disoproxil fumarate and didanosine at a dose of 400 mg daily has been associated with a significant decrease in CD4 cell count, possibly due to an intracellular interaction increasing phosphorylated (i.e. active) didanosine leading to cytotoxic effects. A decreased dosage of 250 mg didanosine co-administered with tenofovir disoproxil fumarate has been associated with reports of high rates of virological failure within several tested combinations for the treatment of HIV-1 infection.

### ***Renal Impairment***

Emtricitabine and tenofovir are primarily excreted by the kidneys, through 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 (see section 4.8).

It is recommended that creatinine clearance/estimated glomerular function be calculated in all individuals prior to initiating therapy and as clinically appropriate during therapy with Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets.

### **Pre-exposure Prophylaxis**

Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets should not be used for PrEP in HIV-1 uninfected individuals with estimated creatinine clearance below 60 ml/min. Creatinine testing should be undertaken quarterly during the first 12 months and annually thereafter. If a decrease in estimated creatinine clearance is observed in uninfected individuals while using this medicine for PrEP, potential causes should be evaluated and potential risks and benefits of continued use re-assessed.

### **HIV-therapy**

If the creatinine test is routinely available, use the estimated glomerular filtration rate at baseline before initiating TDF regimens.

Benefits and risks should be carefully weighted when initiating TDF in patients with an estimated glomerular filtration rate <50 ml/min, or in long-term diabetes, uncontrolled hypertension and renal failure (see section 4.2).

If the creatinine test is not routinely available, urine dipsticks may be used to detect glycosuria or severe TDF nephrotoxicity in individuals without risk factors.

Creatinine testing is particularly advisable for high-risk people (those who are older or have underlying renal disease, long-term diabetes or uncontrolled hypertension concomitant with boosted PIs or nephrotoxic drugs) to detect and limit further progression of renal impairment. If available, also serum phosphate should be measured in these patients.

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/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets, 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 TDF in patients with creatinine clearance decreased to < 50 ml/min or decreases in serum phosphate below 1.0 mg/dl (0.32 mmol/l). Interrupting treatment with Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets should also be considered in case of progressive decline of renal function when no other cause has been identified.

The renal safety of tenofovir disoproxil fumarate taken together with emtricitabine 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 fumarate 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/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets 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/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets at a prolonged dosing interval. The use of this medicine is not recommended in patients with

severe renal impairment (creatinine clearance < 30 ml/min) and in patients who require haemodialysis.

Use of tenofovir disoproxil fumarate should be avoided with concurrent use of a nephrotoxic medicinal product (e.g. high-dose or multiple non-steroidal anti-inflammatory drugs, aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2). If concomitant use of tenofovir disoproxil fumarate and nephrotoxic agents is unavoidable, renal function should be monitored weekly.

### ***Bone effects***

In a controlled clinical study decreases in bone mineral density of spine and changes in bone biomarkers from baseline were observed in both treatment groups, but were significantly greater in the tenofovir disoproxil fumarate treatment group than in the comparator group treated with stavudine (each in combination with lamivudine and efavirenz) at 144 weeks. Decreases in bone mineral density of the hip were significantly greater in this group until 96 weeks. However, there was no increased risk of fractures or evidence for clinically relevant bone abnormalities over 144 weeks.

Bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy (see section 4.8). If bone abnormalities are suspected then appropriate consultation should be obtained.

### ***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 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/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets have not been established for the treatment of chronic HBV infection. Emtricitabine and tenofovir individually and in combination have shown activity against HBV (see section 5.1). 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/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets 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 it 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/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets have not been established in patients with significant underlying liver disorders (see also sections 4.2 and 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 toxicity***

Nucleoside and nucleotide analogues have been demonstrated, *in vitro* and *in vivo*, to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed *in utero* and/or postnatally to nucleoside analogues. The main adverse events reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactataemia, hyperlipasaemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether the neurological disorders are transient or permanent is currently unknown.

Any child exposed *in utero* to nucleoside and nucleotide analogues, even HIV-negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms.

These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

### ***Immune Reactivation Syndrome***

In HIV-infected patients with pre-existing severe immune deficiency, typically in the first few weeks or months after initiation of CART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens (e.g. CMV retinitis, mycobacterial infections, Pneumocystis pneumonia) may arise and cause serious clinical conditions or aggravation of symptoms. Treatment should be instituted when necessary.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillan-Barré syndrome) 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***

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

### ***Elderly***

The combination of emtricitabine and tenofovir 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/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets.

### ***Excipients***

Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption may experience symptoms of intolerance when using it.

## **4.5 Interaction with other medicinal products and other forms of interaction**

As Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets contains emtricitabine and tenofovir disoproxil fumarate, any interactions that have been identified with these agents individually may occur with Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets. Interaction studies have only been performed in healthy adult volunteers.

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

*In vitro* and clinical pharmacokinetic interaction studies have shown the potential for cytochrome P450 mediated interactions involving emtricitabine and tenofovir disoproxil fumarate with other medicinal products is low.

### ***Concomitant use not recommended***

Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets should not be administered with any other medicinal products containing tenofovir disoproxil fumarate, tenofovir alafenamide, adefovir dipivoxil, emtricitabine or lamivudine (see section 4.4 and below).

### ***Interactions relevant to 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, and did not inhibit enzymatic glucuronidation. There are no clinically significant interactions when emtricitabine is co-administered with indinavir, zidovudine, stavudine, famciclovir or tenofovir. Emtricitabine is primarily excreted via glomerular

filtration and active tubular secretion. With the exception of famciclovir and tenofovir disoproxil fumarate, the effect of co-administration of emtricitabine with medicinal products that are excreted by the renal route, or other medicinal products known to affect renal function, has not been evaluated.

Co-administration of Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets with medicinal products that reduce renal function or are eliminated by active tubular secretion may lead to an increase in serum concentrations of either emtricitabine or a co-administered medicinal product due to competition for this elimination pathway.

Use of Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets 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, acyclovir, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2 and high-dose or multiple non-steroidal anti-inflammatory drugs. There is no clinical experience or virologic rationale for the co-administration of emtricitabine and cytidine analogues. Consequently, Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets should not be administered in combination with lamivudine for the treatment of HIV infection (see section 4.4).

#### ***Interactions relevant to tenofovir***

##### **Didanosine**

Co-administration of Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets and didanosine is not recommended (see section 4.4 and Table 2).

Renally eliminated medicinal products

Since tenofovir is primarily eliminated by the kidneys, co-administration of Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets with medicinal products that reduce renal function or compete for active tubular secretion via transport proteins hOAT 1, hOAT 3 or MRP 4 (e.g. cidofovir) may increase serum concentrations of tenofovir and/or the co-administered medicinal products.

Use of Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets should be avoided with concurrent use of a nephrotoxic medicinal product. Some examples include aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2 (see section 4.4).

#### ***Other interactions***

Interactions between tenofovir disoproxil fumarate and HIV protease inhibitors, as well as antiviral agents other than protease inhibitors, are listed in Table 1 below (increased exposure is indicated as “↑”, decreased exposure as “↓”, no change as “↔”, twice daily as “b.i.d.”, and once daily as “q.d.”).

Table 2: Interactions between tenofovir disoproxil fumarate and other medicinal products

<b>Medicinal products by therapeutic areas (dose in mg)</b>	<b>Effects on drug levels Mean % change in AUC, C<sub>max</sub>, C<sub>min</sub></b>	<b>Recommendation concerning co-administration Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/ 300 mg Tablets</b>
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# Tenofovir Disoproxil Fumarate/Emtricitabine Tablets 300 mg/200 mg

ANTI-INFECTIVES		
Antiretrovirals		
Protease inhibitors		
Atazanavir (400 mg q.d.)	<p>Atazanavir: AUC: ↓ 25% C<sub>max</sub>: ↓ 21% C<sub>min</sub>: ↓ 40%</p> <p>Tenofovir: AUC: ↑ 24% C<sub>max</sub>: ↑ 14% C<sub>min</sub>: ↑ 22%</p>	If atazanavir and Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets are coadministered, atazanavir should be given at the dose 300 mg q.d. together with ritonavir 100 mg q.d. ("ritonavir-boosting", see below)
Atazanavir/ritonavir (300 mg q.d./100 mg q.d.)	<p>Atazanavir: AUC: ↓ 25% C<sub>max</sub>: ↓ 28% C<sub>min</sub>: ↓ 26%</p> <p>Tenofovir: AUC: ↑ 37% C<sub>max</sub>: ↑ 34% C<sub>min</sub>: ↑ 29%</p>	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir associated adverse events, including renal disorders. Renal function should be closely monitored (see section 4.4).
Lopinavir/ritonavir (400/100 mg b.i.d.)	<p>Lopinavir/ritonavir: No significant effect on lopinavir/ritonavir PK parameters.</p> <p>Tenofovir: AUC: ↑ 32% C<sub>max</sub>: ↔ C<sub>min</sub>: ↑ 51%</p>	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir associated adverse events, including renal disorders. Renal function should be closely monitored (see section 4.4).
Darunavir/ritonavir (300/100 mg b.i.d.)	<p>Darunavir: No significant effect on darunavir/ritonavir PK parameters.</p> <p>Tenofovir: AUC: ↑ 22% C<sub>min</sub>: ↑ 37%</p>	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir associated adverse events, including renal disorders. Renal function should be closely monitored (see section 4.4).
NRTIs		
Didanosine (400 mg q.d.)	Didanosine AUC ↑ 40-60%	The risk of didanosine-related adverse effects (e.g., pancreatitis, lactic acidosis appears to be increased, and CD4 cells may decrease significantly on co-administration. Didanosine at 250 mg co-administered with tenofovir within several different antiretroviral combination regimens has been

		associated with a high rate of virological failure. Co-administration of Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets and didanosine is not recommended (see section 4.4).
Entecavir (1 mg q.d.)	AUC: $\leftrightarrow$ C <sub>max</sub> : $\leftrightarrow$	No clinically significant pharmacokinetic interactions when tenofovir disoproxil fumarate was co-administered with entecavir.

*Studies conducted with other medicinal products:* There were no clinically significant pharmacokinetic interactions when tenofovir disoproxil fumarate was co-administered with emtricitabine, lamivudine, indinavir, efavirenz, saquinavir (ritonavir boosted), methadone, ribavirin, rifampicin, tacrolimus, or the hormonal contraceptive norgestimate/ethinyl oestradiol.

### ***Food effect***

Food has no influence on the absorption of emtricitabine and enhances the bioavailability of tenofovir (see sections 4.2 and 5.2).

## **4.6 Fertility, pregnancy and lactation**

### ***Pregnancy***

Animal studies do not indicate reproductive toxicity of tenofovir disoproxil fumarate or emtricitabine (see section 5.3). Sufficient numbers of first trimester exposures have been monitored to detect at least a twofold increase in the risk of overall birth defects. No increase in birth defects was seen ([www.apregistry.com](http://www.apregistry.com)).

The use of Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets may be considered during pregnancy.

### ***Breastfeeding***

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. A risk to the suckling child cannot be excluded.

Current recommendations on HIV and breastfeeding (e.g. those from the WHO) should be consulted before advising patients on this matter. Preferred options may vary depending on the local circumstances.

### ***Fertility***

Clinical data on the effect of tenofovir disoproxil fumarate on fertility are limited. Animal studies do not indicate harmful effects of emtricitabine and tenofovir disoproxil fumarate on fertility.

#### **4.7 Effects on ability to drive and use machines**

No studies on the effects on the ability to drive and use machines have been performed. However, patients should be informed that dizziness has been reported during treatment with tenofovir disoproxil fumarate and emtricitabine.

#### **4.8 Undesirable effects**

##### ***HIV-therapy***

In a trial for treatment of HIV infection, 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 safety profile of emtricitabine and tenofovir disoproxil fumarate 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 fumarate, rare events of renal impairment, renal failure and proximal renal tubulopathy (including Fanconi syndrome) sometimes leading to bone abnormalities (infrequently contributing to fractures) have been reported. Monitoring of renal function is recommended for patients receiving Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets (see section 4.4).

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

Discontinuation of Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis (see section 4.4).

The adverse reactions considered at least possibly related to treatment with the components of Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets 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 ( $\geq 1/10$ ), common ( $\geq 1/100$ ,  $< 1/10$ ), uncommon ( $\geq 1/1,000$ ,  $< 1/100$ ), rare ( $\geq 1/10,000$ ,  $< 1/1,000$ ) or very rare ( $< 1/10,000$ ) including isolated reports, 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 (common in paediatric patients)

##### **Immune system disorders:**

Common: allergic reaction

**Metabolism and nutrition disorders:**

Very common: hypophosphataemia

Common: hyperglycaemia, hypertriglyceridaemia

Rare: lactic acidosis

Not known: hypokalaemia

**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: hepatic steatosis, hepatitis

**Skin and subcutaneous tissue disorders:**

Very common: rash

Common: urticaria, vesiculobullous rash, pustular rash, maculopapular rash, pruritus, rash and skin discolouration (increased pigmentation – very common in children)

**Musculoskeletal and connective tissue disorders:**

Very common: elevated creatine kinase

Uncommon: rhabdomyolysis, muscular weakness

Rare: osteomalacia (manifested as bone pain and infrequently contributing to fractures), myopathy

**Renal and urinary disorders:**

Uncommon: increased creatinine, proteinuria

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

Very rare: acute tubular necrosis, nephritis (including acute interstitial nephritis), nephrogenic diabetes insipidus.

**General disorders and administration site conditions:**

Common: pain, asthenia

Not known: Immune reconstitution syndrome

***Pre-exposure prophylaxis***

## Tenofovir Disoproxil Fumarate/Emtricitabine Tablets 300 mg/200 mg

In two randomised controlled HIV-prevention trials in men who have sex with men, transgender women (iPrEx trial) and serodiscordant couples (PartnersPrEP), in which 2830 uninfected adults received fixed dose combination tablets of emtricitabine and tenofovir DF no new adverse reactions were reported. Of those reactions, occurring in at least 2% of subjects, the following were reported more frequently in the treatment group (as compared to placebo, all from iPrEx-trial).

- Headache (7% vs. 6%)
- Syphilis 6% vs. 5%, secondary syphilis (6% vs. 4%)
- Abdominal pain (4% versus 2%)
- Weight decreased (3% vs, 2%).

The following laboratory abnormalities were reported in these trials.

	Grade <sup>b</sup>	iPrEx Trial		Partners PrEP Trial	
		FTC/TDF N=1251	Placebo N=1248	FTC/TDF N=1579	Placebo N=1548
Creatinine	1 (1.1-1.3 x ULN)	27 (2%)	21 (2%)	18 (1%)	12 (<1%)
	2-4 (>1.4 x ULN)	5 (<1%)	3 (<1%)	2 (<1%)	1 (<1%)
Phosphorus	1 (2.5 - <LLN mg/dl)	81 (7%)	110 (9%)	NR <sup>a</sup>	NR <sup>a</sup>
	2-4 (<2.5 mg/dl)	123 (10%)	101 (8%)	140 (9%)	136 (9%)
AST	1 (1.25 - <2.5 x ULN)	175 (14%)	175 (14%)	20 (1%)	25 (2%)
	2-4 (> 2.6 x ULN)	57 (5%)	61 (5%)	10 (<1%)	4 (<1%)
ALT	1 (1.25 - <2.5 x ULN)	178 (14%)	194 (16%)	21 (1%)	25 (2%)
	2-4 (> 2.6 x ULN)	84 (7%)	82 (7%)	4 (<1%)	6 (<1%)
Haemoglobin	1 (8.5-10 mg/dl)	49 (4%)	62 (5%)	56 (4%)	39 (2%)
	2-4 (< 8.4 mg/dl)	13 (1%)	19 (2%)	28 (2%)	39 (2%)
Neutrophils	1 (1000-1300/mm <sup>3</sup> )	23 (2%)	25 (2%)	208 (13%)	13 (10%)
	2-4 (< 750 mm <sup>3</sup> )	7 (<1%)	7 (<1%)	73 (5%)	56 (3%)

a. Grade 1 phosphorus was not reported for the Partners PrEP trial

b. Grading is per DAIDS criteria

In addition to the laboratory abnormalities described above, grade 1 proteinuria occurred in 6% of subjects receiving emtricitabine/tenofovir DF in the iPrEx trial. Grades 2-3 proteinuria and glycosuria occurred in less than 1% of subjects treated with emtricitabine/tenofovir DF in the iPrEx trial and PartnersPrEP trial.

Six subjects in the TDF-containing arms of the Partners PrEP trial discontinued participation in the study due to an increase in blood creatinine compared with no discontinuations in the placebo group. One subject in the emtricitabine/tenofovir DF arm of the iPrEx trial discontinued from the study due to an increase in blood creatinine and another due to low phosphorous.

### Changes in Bone Mineral Density

In clinical trials of HIV-1 uninfected individuals, decreases in BMD were observed. In the iPrEx trial, a substudy of 503 subjects found mean changes from baseline in BMD ranging from -0.4% to -1.0% across total hip, spine, femoral neck, and trochanter in the emtricitabine/tenofovir DF group compared with the placebo group, which returned toward baseline after discontinuation of treatment. Thirteen percent of subjects receiving emtricitabine/tenofovir DF vs. 6% of subjects receiving placebo lost at least 5% of BMD at the spine during treatment. Bone fractures were reported in 1.7% of the emtricitabine/tenofovir DF group compared with 1.4% in the placebo group.

No correlation between BMD and fractures was noted (see 5.1 Clinical results). The Partners PrEP trial found similar fracture rates between treatment and placebo groups (0.8% and 0.6%, respectively). No BMD evaluations were conducted during this trial.

### ***Description of selected adverse reactions***

#### **Renal impairment**

As Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets 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 fumarate discontinuation. However, in some patients, declines in creatinine clearance did not completely resolve despite tenofovir disoproxil fumarate 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 fumarate discontinuation (see section 4.4).

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 likely to be causally associated with tenofovir disoproxil fumarate therapy in the absence of proximal renal tubulopathy.

#### **Interaction with didanosine**

Co-administration of tenofovir disoproxil fumarate and didanosine is not recommended as it results in a 40-60% increase in systemic exposure to didanosine that may increase the risk of didanosine-related adverse reactions. (see section 4.5). Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported.

#### **Metabolic parameters**

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

#### **Lipids, lipodystrophy and metabolic abnormalities**

CART has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see section 4.4).

CART has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump) (see section 4.4).

#### **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) have also been reported; 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**

Safety data from studies using the combination tablet in patients less than 10 years of age are not available. In studies with emtricitabine in addition to the adverse reactions reported in adults, the following adverse reactions were observed more frequently in paediatric patients: anaemia was common (9.5%) and skin discolouration (increased pigmentation) was very common (31.8%).

The adverse reactions observed in paediatric patients who received treatment with tenofovir disoproxil fumarate were consistent with those observed in clinical studies of tenofovir disoproxil fumarate in adults

### **Other special population(s)**

#### *Elderly*

Emtricitabine/tenofovir 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/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets.

#### *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 the abovementioned study. 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, elevations in AST and ALT occurred more frequently than in the general HIV infected population. In HIV-negative individuals limited data indicate that the adverse reaction profile of emtricitabine and tenofovir disoproxil fumarate was similar in individuals with and without hepatitis B/C infection.

## **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. Tenofovir and emtricitabine 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 infection, combinations. ATC code: J05AR03

#### ***Mechanism of action and pharmacodynamic effects***

Emtricitabine is an analogue of the nucleoside cytidine. Tenofovir disoproxil fumarate is converted *in vivo* to tenofovir, a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate. Emtricitabine and tenofovir are phosphorylated by cellular enzymes to form

emtricitabine triphosphate and tenofovir diphosphate, respectively. Emtricitabine triphosphate and tenofovir diphosphate competitively inhibit HIV-1 reverse transcriptase (RT), resulting in DNA chain termination. Both substances are active against HIV-1 and HIV-2, as well as against hepatitis B virus. Clinical results:

### ***HIV therapy***

When tenofovir and emtricitabine were combined with efavirenz in treatment-naïve patients with HIV-, the proportion of patients (ITT) with HIV-RNA <50 copies/ml were 80 and 64% at 48 and 144 weeks, respectively. In another study, where tenofovir and emtricitabine were combined with lopinavir/ritonavir given once or twice daily in treatment naïve patients, 70% and 64% of patients demonstrated HIV-1 RNA < 50 copies/ml with the once and twice daily regimens of lopinavir/ritonavir, respectively.

### ***Pre-exposure Prophylaxis***

In a primary prevention trial (iPrEX), designed to evaluate the safety and efficacy of once-daily oral tenofovir-emtricitabine compared with placebo for the prevention of HIV acquisition among men who have sex with men and among transgender women both having evidence of high risk behaviour for HIV-1 infection, use of pre-exposure prophylaxis with a median follow-up time of 1.2 years was associated with reduced risk of new HIV infection in both intention-to-treat analysis (HR: 0.53, 95% CI 0.36–0.78, p=0.001) and modified intention-to-treat analysis (HR: 0.56, 95% CI 0.37–0.85, p<0.001).

In the Partners PrEP trial, conducted in serodiscordant heterosexual couples to evaluate the efficacy and safety of tenofovir and emtricitabine/tenofovir versus placebo, in preventing HIV-1 acquisition by the uninfected partner, the risk reduction for emtricitabine/tenofovir relative to placebo was 75% (HR: 0.25, 95% CI: 0.55-0.87, p=0.005) following 7827 person-years of follow-up.

In a post-hoc case control study of plasma drug levels in about 10% of study subjects, risk reduction appeared to be the greatest in subjects with detectable plasma tenofovir. Efficacy was therefore strongly correlated with adherence.

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 log<sub>10</sub> reduction or 4 to 5 log<sub>10</sub> reduction, respectively) (see section 4.4).

### ***Resistance***

The K65R mutation is selected *in vitro* when HIV-1 is cultured in the presence of increasing tenofovir concentrations. It may also emerge *in vivo* upon virological failure of a treatment regimen including tenofovir. K65R reduces tenofovir susceptibility *in vitro* approximately 2-fold, and has been associated with a lack of response to tenofovir-containing regimens. Clinical studies in treatment-experienced patients have assessed the anti-HIV activity of tenofovir against strains of HIV-1 with thymidine analogue mutations (TAMs), which are not selected for by tenofovir. 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. Viruses that expressed 3

or more thymidine-analogue associated mutations (TAMs) that included either the M41L or L210W RT mutation showed reduced response to tenofovir.

HIV-1 resistance to emtricitabine develops as the result of the M184V mutation in the RT. This HIV-1 mutation was observed *in vitro* and in HIV-1 infected patients in primary prevention trials. A case of tenofovir resistance involving virus expressing the combination of D67N and K70R substitutions has been observed, but it is unclear whether this mutation is naturally transmitted or it emerged during therapy with emtricitabine/tenofovir DF. Emtricitabine-resistant viruses were cross-resistant to lamivudine, but retained sensitivity to other nucleoside reverse transcriptase inhibitors (NRTIs) (zidovudine, stavudine, tenofovir, abacavir, didanosine and zalcitabine), all non-nucleoside reverse transcriptase inhibitors (NNRTIs) and all protease inhibitors (PIs).

In two clinical studies of HIV-1 seronegative subjects [iPrEx Trial, PartnersPrEP Trial], no amino acid substitutions associated with resistance to emtricitabine or tenofovir were detected at the time of seroconversion among 60 subjects in the emtricitabine/tenofovir DF groups and 134 subjects in the placebo groups who became infected with HIV-1 during the trial.

## **5.2 Pharmacokinetic properties**

### ***Absorption***

Following oral administration of emtricitabine/tenofovir disoproxil fumarate to HIV infected patients, emtricitabine and tenofovir disoproxil fumarate are rapidly absorbed and tenofovir disoproxil fumarate is converted to tenofovir. Tenofovir is converted intracellularly to tenofovir monophosphate and to the active component, tenofovir diphosphate.

Following single dose administration of Emtricitabine/Tenofovir Disoproxil Fumarate 200mg/300 mg Tablets in healthy volunteers, the mean ( $\pm$  SD) tenofovir  $C_{max}$  value was 311 ng/ml ( $\pm$  87) the corresponding value for AUC was 1563 ng.h/ml ( $\pm$ 572); the mean ( $\pm$ SD) emtricitabine  $C_{max}$  value was 1737 ng/ml ( $\pm$ 425) and the corresponding value for AUC was 8123 ng.h/ml ( $\pm$ 1541). The mean ( $\pm$ SD) tenofovir  $T_{max}$  value was 0.96 ( $\pm$ 0.27) hours and for emtricitabine it was 1.45 ( $\pm$ 0.59) hours.

The oral bioavailability of tenofovir from tenofovir disoproxil fumarate in fasted patients was approximately 25%. Administration of tenofovir disoproxil fumarate with a high fat meal enhanced the oral bioavailability, with an increase in tenofovir AUC by approximately 35% and  $C_{max}$  by approximately 15%. Administration of tenofovir disoproxil fumarate with a light meal had a smaller effect on the pharmacokinetics of tenofovir.

### ***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  $\mu$ g/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  $\mu$ g/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.

### ***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.

### ***Special populations***

#### **Older people**

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

#### **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 fixed dose combination 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%)  $\mu\text{g}\cdot\text{h}/\text{ml}$  in subjects with normal renal function, to 20 (6%)  $\mu\text{g}\cdot\text{h}/\text{ml}$ , 25 (23%)  $\mu\text{g}\cdot\text{h}/\text{ml}$  and 34 (6%)  $\mu\text{g}\cdot\text{h}/\text{ml}$ , in patients with mild, moderate and severe renal impairment, respectively.

The mean (%CV) tenofovir drug exposure increased from 2,185 (12%)  $\text{ng}\cdot\text{h}/\text{ml}$  in patients with normal renal function, to 3,064 (30%)  $\text{ng}\cdot\text{h}/\text{ml}$ , 6,009 (42%)  $\text{ng}\cdot\text{h}/\text{ml}$  and 15,985 (45%)  $\text{ng}\cdot\text{h}/\text{ml}$ , in patients with mild, moderate and severe renal impairment, respectively.

The increased dose interval for Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets in patients with moderate renal impairment is expected to result in higher peak plasma concentrations and lower C<sub>min</sub> 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%)  $\mu\text{g}\cdot\text{h}/\text{ml}$  of emtricitabine, and over 48 hours to 42,857 (29%)  $\text{ng}\cdot\text{h}/\text{ml}$  of tenofovir.

It is recommended that the dosing interval for Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets is modified in patients with creatinine clearance between 30 and 49 ml/min. Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets 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 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 tenofovir DF/ emtricitabine as fixed dose combination have not been studied in patients with hepatic impairment. However, it is unlikely that a dose adjustment would be required for Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets 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.

### **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**

#### ***Core tablet***

Croscarmellose sodium  
Lactose monohydrate  
Magnesium stearate  
Microcrystalline cellulose

***Film coat***

FD&C Blue#2, hypromellose, lactose monohydrate, titanium dioxide and triacetin

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

24 months in blisters.

36 months in bottles.

**6.4 Special precautions for storage**

Do not store above 30°C. Store in the original container.

**6.5 Nature and contents of container**

3 Blisters of 10's

Bottle of 30's & 100's.

**6.6 Special precautions for disposal**

No special requirements.

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

Safe disposal instructions about the desiccant: dessicant bag or its contents must not chewed, swallowed or torn. It should be disposed off intact.

**7. MARKET AUTHORIZATION HOLDER**

**Mylan Laboratories Limited**

**REFERENCES**

General reference sources for this SmPC include:

WHO guidelines on treatment and pre-exposure prophylaxis of HIV-infection, available at <http://www.who.int/hiv/pub/guidelines/arv2013/download/en/>

and <http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en/>

European SmPC Truvada, available at:

[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/000594/WC500043718.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000594/WC500043718.pdf)

Truvada, US prescribing information, available at

## Tenofovir Disoproxil Fumarate/Emtricitabine Tablets 300 mg/200 mg

[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/021752s050lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021752s050lbl.pdf)

European SmPC Viread, available at:

[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/000419/WC500051737.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000419/WC500051737.pdf)

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All weblinks were last accessed 05 June 2016

Zambia Regn No.: 014/005

Zimbabwe Regn No.: 2011/7.13/4675

Botswana Regn No.: BOT 0801489

POM

Schedule 2

PP

List - 1



**Manufactured by**

**Mylan Laboratories Limited**

F-4 & F-12, MIDC, Malegaon, Sinnar,  
Nashik - 422 113, Maharashtra, INDIA