5. Summary of Product Characteristics

SUMMARY OF PRODUCT CHARACTERISTICS

TENOFOVIR & EMTRICITABINE TABLETS

1. NAME OF THE MEDICINAL PRODUCT

TAVIN — EM

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

Emtricitabine 200 mg

Tenofovir Disoproxil Fumarate 300 mg

3. PHARMACEUTICAL FORM

Film-coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic **indications**

This product is indicated in combination with other antiretroviral agents (such as non-nucleoside reverse transcriptase inhibitors or protease inhibitors) for the treatment of HIV-1 infection in adults.

4.2 Posology and method of administration

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

Treatment of HIV in adults and adolescents aged 12 years and older, weighing at least 35 kg: One tablet, once daily.

Prevention of HIV in adults: One tablet, once daily. Separate preparations of emtricitabine and tenofovir disoproxil fumarate are available for treatment of HIV-1 infection if it becomes necessary to discontinue or modify the dose of one of the components of Tavin-Em. Please refer to the Summary of Product Characteristics for these medicinal products. If a dose of Tavin-Em is missed within 12 hours of the time it is usually taken, Tavin-Em should be taken as soon as possible and the normal dosing schedule should be resumed. If a dose of Tavin-Em is missed 3 by more than 12 hours and it is almost time for the next dose, the missed dose should not be taken and the usual dosing schedule should be resumed. If vomiting occurs within 1 hour of taking Tavin-Em, another tablet should be taken. If vomiting occurs more than 1 hour after taking Tavin-Em a second dose should not be taken.

Special populations

Elderly: No dose adjustment is required (see section 5.2). Renal impairment: Emtricitabine and tenofovir are eliminated by renal excretion and the exposure to emtricitabine and tenofovir increases in

individuals with renal dysfunction (see sections 4.4 and 5.2).
Adults with renal impairment: Tavin-Em should only be used in individuals with creatinine clearance (CrCl) < 80 mL/min if the potential benefits are considered to outweigh the potential risks. See Table 1.

Table 1: Dosing recommendations in adults with renal impairment Treatment of HIV-1 infection Pre-exposure prophylaxis

Mild renal impairment (CrCl 50-80 mL/min) Limited data from clinical studies support once daily dosing of Tavin-Em (see section 4.4). Limited data from clinical studies support once daily dosing of Tavin-Em in HIV-1 uninfected individuals with CrCl 60-80 mL/min. Tavin-Em is not recommended for use in HIV-1 uninfected individuals with CrCl < 60 mL/min as it has not been studied in this population (see sections 4.4 and 5.2).

Moderate renal impairment (CrCl 30-49 mL/min) Administration of Tavin-Em 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). Tavin-Em is not recommended for use in this population.

Severe renal impairment (CrCl < 30 mL/min) and haemodialysis patients Tavin -Em is not recommended because appropriate dose reductions cannot be achieved with the combination tablet. Tavin-Em is not recommended for use in this population.

Paediatrics with renal impairment: Use of Tavin-Em is not recommended in HIV-1 infected paediatric patients under the age of 18 years with renal impairment (see section 4.4).

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

Paediatric population: The safety and efficacy of Tavin -Em in children under the age of 12 years have not been established (see section 5.2).

Method of administration
Oral administration. It is preferable that Tavin-Em is taken with food. Tavin –Em can be disintegrated in 100ml of water, orange juice, grape juice and taken immediately.

4.3 Contraindications

This product is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the product.

4.4 Special warnings and precautions for use

General

Transmission of HIV: While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines. Patients with HIV-1 harbouring mutations Tavin-em should be avoided in antiretroviral-experienced patients with HIV-1 harbouring the K65R mutation (see section 5.1). Overall HIV-1 infection prevention strategy Tavin – em is not always effective in preventing the acquisition of HIV-1. The time to onset of protection after commencing Tavin-em is unknown. Tavin-em should only be used for pre-exposure prophylaxis as part of an overall HIV-1 infection prevention strategy including the use of other HIV-1 prevention measures (e.g. consistent and correct condom use, knowledge of HIV-1 status, regular testing for other sexually transmitted infections).

Risk of resistance with undetected HIV-1 infection: Tavin-em should only be used to reduce the risk of acquiring HIV-1 in individuals confirmed to be HIV negative (see section 4.3). Individuals should be re-confirmed to be HIV-negative at frequent intervals (e.g. at least every 3 months) using a combined antigen/antibody test while taking Tavin-em for pre-exposure prophylaxis. Tavin-em alone does not constitute a complete regimen for the treatment of HIV-1 and HIV-1 resistance mutations have emerged in individuals with undetected HIV-1 infection who are only taking Tavin-em. If clinical symptoms consistent with acute viral infection are present and recent (< 1 month) exposures to HIV-1 are suspected, use of Tavin-em should be delayed for at least one month and HIV-1 status reconfirmed before starting Tavin-em for pre-exposure prophylaxis.

Importance of adherence:

HIV-1 uninfected individuals should be counselled to strictly adhere to the recommended Tavin-em dosing schedule. The effectiveness of Tavin-em in reducing the risk of acquiring HIV-1 is strongly correlated with adherence as demonstrated by measurable drug levels in blood.

Patients with hepatitis B or C virus infection

HIV-1 infected 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 management of HIV infection in patients co-infected with hepatitis B virus (HBV) or hepatitis C virus (HCV). 5

The safety and efficacy of Tavin-em for PrEP in patients with HBV or HCV infection has not been established. 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. See also under Use with ledipasvir and sofosbuvir below.

Tenofovir (disoproxil fumarate) is indicated for the treatment of HBV and emtricitabine has shown activity against HBV in pharmacodynamic studies but the safety and efficacy of Tavin-em have not been specifically established in patients with chronic HBV infection.

Discontinuation of Tavin-em therapy in patients infected with HBV may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue Tavin-em 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 Tavin-em have not been established in patients with significant underlying liver disorders. The pharmacokinetics of tenofovir has been studied in patients with hepatic impairment and no dose adjustment is required. 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 Tavin-em in patients with hepatic impairment (see sections 4.2 and 5.2). HIV-1infected 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.

Renal and bone effects in adults

Renal effects 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 (see section 4.8).

Renal monitoring

Prior to initiating Tavin-em for the treatment of HIV-1 infection or for use in pre-exposure prophylaxis, it is recommended that creatinine clearance is calculated in all individuals.

In individuals without risk factors for renal disease, it is recommended that renal function (creatinine clearance and serum phosphate) is monitored after two to four weeks of use, after three months of use and every three to six months thereafter.

In individuals at risk for renal disease more frequent monitoring of renal function is required.

See also under Co-administration of other medicinal products below.

Renal management in HIV-1 infected 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 Tavin-em, 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 be given to interrupting treatment with Tavin-em in 6 patients with creatinine clearance decreased to < 50 mL/min or decreases in serum phosphate to < 1.0 mg/dL (0.32 mmol/L). Interrupting treatment with Tavin-em should also be considered in case of progressive decline of renal function when no other cause has been identified. Renal safety with Tavin-em has only been studied to a very limited degree in HIV-1 infected patients with impaired renal function (creatinine clearance < 80 mL/min). Dose interval adjustments are recommended for HIV-1 infected 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 Tavin-em 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 Tavin-em at a prolonged dosing interval. The use of Tavin-em is not recommended in patients with severe renal impairment (creatinine clearance < 30 mL/min) and in patients who require haemodialysis since appropriate dose reductions cannot be achieved with the combination tablet (see sections 4.2 and 5.2).

Renal management in PrEP:

Tavin-em has not been studied in HIV-1 uninfected individuals with creatinine clearance < 60 mL/min and is therefore not recommended for use in this population. If serum phosphate is < 1.5 mg/dL (0.48 mmol/L) or creatinine clearance is decreased to < 60 mL/min in any individual receiving Tavin-em for pre-exposure prophylaxis, 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 be given to interrupting use of with Tavin -em in individuals with creatinine clearance decreased to < 60 mL/min or decreases in serum phosphate to < 1.0 mg/dL (0.32 mmol/L). Interrupting use of Tavin-em should also be considered in case of progressive decline of renal function when no other cause has been identified.

Bone effects: 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.

HIV-1 infection:

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 (BMD) of the hip and spine were observed in both treatment groups. Decreases in BMD of spine and changes in bone biomarkers from baseline were significantly greater in the tenofovir disoproxil fumarate treatment group at 144 weeks. Decreases in BMD of hip were significantly greater in this group until 96 weeks. However, there was no increased risk of fractures or evidence for clinically relevant bone abnormalities over 144 weeks. In other studies (prospective and cross-sectional), the most pronounced decreases in BMD were seen in patients treated with tenofovir disoproxil fumarate as part of a regimen containing a boosted protease inhibitor. Alternative treatment regimens should be considered for patients with osteoporosis that are at a high risk for fractures.

Tavin-em for PrEP: In clinical studies of HIV-1 uninfected individuals, small decreases in BMD were observed. In a study of 498 men, the mean changes from baseline to week 24 in BMD ranged from -0.4% to -1.0% across hip, spine, femoral neck and trochanter in men who received daily Tavin-em prophylaxis (n = 247) vs. placebo (n = 251). 7

Renal and bone effects in the paediatric population

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

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

Renal monitoring

Renal function (creatinine clearance and serum phosphate) should be evaluated prior to treatment, and monitored during treatment as in HIV-1 infected adults (see above).

Renal management If serum phosphate is confirmed to be < 3.0 mg/dl (0.96 mmol/l) in any paediatric patient receiving Tavin-em renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations (see section 4.8,

proximal tubulopathy). If renal abnormalities are suspected or detected then consultation with a nephrologist should be obtained to consider interruption of treatment. Interrupting treatment with Truvada should also be considered in case of progressive decline of renal function when no other cause has been identified.

Co-administration and risk of renal toxicity

The same recommendations apply as in adults (see Co-administration of other medicinal products below).

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

Bone effects

Tenofovir disoproxil fumarate may cause a reduction in BMD. The effects of tenofovir disoproxil fumarate-associated changes in BMD on long-term bone health and future fracture risk are currently unknown (see section 5.1). If bone abnormalities are detected or suspected in paediatric patients, consultation with an endocrinologist and/or nephrologist should be obtained.

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

Mitochondrial dysfunction following exposure in utero Nucleos(t)ide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV negative infants exposed in utero and/or postnatally to nucleoside analogues; these have predominantly concerned treatment with regimens containing zidovudine. The main adverse reactions reported are haematological disorders (anaemia, neutropenia) and metabolic disorders 8 (hyperlactatemia, hyperlipasemia). These events have often been transitory. Late onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently unknown. These findings should be considered for any child exposed in utero to nucleos(t)ide analogues, who present with severe clinical findings of unknown etiology, particularly neurologic findings. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Immune Reactivation Syndrome

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

Opportunistic infections

HIV-1 infected patients receiving Tavin-em 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.

Osteonecrosis

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

Co-administration of other medicinal products

Use of Tavin-em should be avoided with concurrent or recent use of a nephrotoxic medicinal product (see section 4.5). If concomitant use of Tavin-em and nephrotoxic agents is unavoidable, renal function should be monitored weekly. Cases of acute renal failure after initiation of high dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs) have been reported in HIV-1 infected patients treated with tenofovir disoproxil fumarate and with risk factors for renal dysfunction. If Tavin-em is co-administered with an NSAID, renal function should be monitored adequately. A higher risk of renal impairment has been reported in HIV-1 infected patients receiving tenofovir disoproxil fumarate in combination with a ritonavir or cobicistat boosted protease inhibitor. Close monitoring of renal function is required in these patients (see section 4.5). In HIV-1 infected patients with renal risk factors, the co-administration of tenofovir disoproxil fumarate with a boosted protease inhibitor should be carefully evaluated. Truvada 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 section 4.5). Tavin-em should not be administered concomitantly with adefovir dipivoxil. 9

Use with ledipasvir and sofosbuvir

Co-administration of tenofovir disoproxil fumarate with ledipasvir/sofosbuvir has been shown to increase plasma concentrations of tenofovir, especially when used together with an HIV regimen containing tenofovir disoproxil fumarate and a pharmacokinetic enhancer (ritonavir or cobicistat). The safety of tenofovir disoproxil fumarate when co-administered with ledipasvir/sofosbuvir and a pharmacokinetic enhancer has not been established. The potential risks and benefits associated with co-administration should be considered, particularly in patients at increased risk of renal dysfunction. Patients receiving ledipasvir/sofosbuvir concomitantly with tenofovir disoproxil fumarate and a boosted HIV protease inhibitor should be monitored for adverse reactions related to tenofovir disoproxil fumarate.

Co-administration of tenofovir disoproxil fumarate and didanosine: Co-administration is not recommended because 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. 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.

Triple nucleoside therapy

There have been reports of a high rate of virological failure and of emergence of resistance at an early stage in HIV-1 infected patients 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 Tavin-em is administered with a third nucleoside analogue.

Elderly ;Tavin-em has not been studied in individuals over the age of 65 years. Individuals over the age of 65 years are more likely to have decreased renal function, therefore caution should be exercised when administering Tavin-em to older people.

Excipients Tavin-em 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.

As Tavin-em contains emtricitabine and tenofovir disoproxil fumarate, any interactions that have been identified with these agents individually may occur with Tavin-em.

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

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

Concomitant use not recommended; Tavin-em 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 section 4.4). Tavin-em should not be administered concomitantly with adefovir dipivoxil.

Didanosine: The co-administration of Tavin-em and didanosine is not recommended (see section 4.4 and Table 2).

Renally eliminated medicinal products: Since emtricitabine and tenofovir are primarily eliminated by the kidneys, co-administration of Tavin-em with medicinal products that

reduce renal function or compete for active tubular secretion (e.g. cidofovir) may increase serum concentrations of emtricitabine, tenofovir and/or the co-administered medicinal products.

Use of Tavin-em should be avoided with concurrent or recent use of a nephrotoxic medicinal product. Some examples include, but are not limited to, aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2 (see section 4.4).

4.6 Pregnancy and lactation

Pregnancy

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

Breast-feeding

Emtricitabine and tenofovir have been shown to be excreted in human milk. There is insufficient information on the effects of emtricitabine and tenofovir in newborns/infants. Therefore Tavin-em should not be used during breast-feeding. As a general rule, it is recommended that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV to the infant.

Fertility

No human data on the effect of Tavin-em are available. Animal studies do not indicate harmful effects of emtricitabine or tenofovir disoproxil fumarate on fertility.

4.7 Effects on ability to drive and use machines

Not known. Dizziness has been reported during treatment with both emtricitabine and tenofovir disoproxil fumarate.

4.8 Undesirable effects

The most frequently reported adverse effects of emtricitabine are mild to moderate headache, nausea, diarrhea, and skin rash. Skin discoloration on palms and soles was reported with higher frequency in emtricitabine-treated patients than in controls, but the mechanism of skin discoloration is unknown. In some patients coinfected with HIV and hepatitis B, exacerbation of hepatitis has been reported after discontinuing treatment with

emtricitabine. Treatment-emergent grade 3 or 4 laboratory abnormalities have been reported in at least 1% of patients receiving emtricitabine. These abnormalities include

triglycerides greater than 750 mg/d1 and creatine kinase over four times the upper limit of normal.

The most common adverse effects associated with tenofovir disoproxil fumarate are asthenia, diarrhea, nausea, and vomiting. Less common side effects of tenofovir disoproxil fumarate are hepatotoxicity, including lactic acidosis; abdominal pain; anorexia; and ftatulence. Some side effects of tenofovir disoproxil fumarate occurring with undetermined incidence include allergic reaction, dyspnea, Fanconi's syndrome, hypophosphatemia, pancreatitis, proximal tubulopathy, renal failure or insufficiency, and acute tubular necrosis. Higher tenofovir concentrations could potentiate tenofovir disoproxil fumarate -associated adverse events, including renal disorders.

4.9 Overdose

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

5.0 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;

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

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

- No virus analysed contained the K65R or K70E mutation.
- Genotypic resistance to efavirenz, predominantly the K103N mutation, developed in virus from 13/19 (68%) patients in the emtricitabine/tenofovir disoproxil fumarate/efavirenz group and in virus from 21/29 (72%) patients in the comparative group.

In vivo -pre-exposure prophylaxis: Plasma samples from 2 clinical studies of HIV-1 uninfected subjects, iPrEx and Partners PrEP, were analysed for 4 HIV-1 variants expressing amino acid substitutions (i.e. K65R, K70E, M184V, and M184I) that potentially confer resistance to tenofovir or emtricitabine.

5.2 Pharmacokinetic properties

Enitricitabine is rapidly and extensively absorbed following oral administration, reaching peak plasma concentrations (Cmax) at 1 to 2 hours. The mean absolute bioavailability of emtricitabine is 93% following multiple doses of the drug. Emtricitabine is less than 4% bound to plasma proteins. Emtricitabine does not inhibit CYP450 enzymes. Biotransformation occurs through glucuronidation and oxidation. Following administration of 14C-emtricitabine, 86% of the dose was recovered in urine and 14% in feces. The plasma half-life of emtricitabine is approximately 10 hours. Renal clearance of the drug exceeds estimated creatinine clearance, indicating elimination by both glomerular filtration and active tubular secretion.

Tenofovir: Oral bioavailability of tenofovir disoproxil fumarate in fasted patients is approximately 25%. Administration of tenofovir disoproxil fumarate with a high fat meal increases the oral bioavailability, with an increase in tenofovir area under the plasma concentration-time curve (AUC) of approximately 40% and an increase in maximum plasma concentration (Cmax) of approximately 14%. Food delays the time to tenofovir Cmax by approximately 1 hour. Following oral administration of a single 300 mg dose of tenofovir disoproxil fumarate to HIV infected patients in the fasted state Cmax is

achieved in approximately 1 hour. The pharmacokinetics of tenofovir is dose proportional over a wide dose range and are not affected by repeat dosing. Binding of tenofovir to human plasma or serum proteins is less than 0.7% and 7.2%, respectively. After multiple oral doses of tenofovir disoproxil fumarate under fed conditions, approximately 32% of the administered dose is recovered in urine over 24 hours. Tenofovir is principally eliminated by the kidneys by a combination of glomerular filtration and active tubular secretion.

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 showed target organ effects in gastrointestinal tract, kidney, bone and a decrease in serum phosphate concentration.

Combination of emtricitabine and tenofovir disoproxil fumarate, found no exacerbation of toxicological effects compared to the separate components.

6.0 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

1) Microcrystalline Cellulose
2) Croscarmellose sodium
3) Pregelatinized starch
4) Lactose Monohydrate
5) Pvidone (PVP K)
6) Magnesium Stearate
7) Isopropyl alcohol
8) Opadry AMB white 80W68912
9) Purified water

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at 20° to 25° C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F).

6.5 Nature and contents of container

30 tablets in a HDPE bottle.

6.6 Special precautions for disposal and other handling

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

7.0 MARKETING AUTHORISATION HOLDER

NAME OF APPLICANT:
EMCURE NIGERIA LIMITED,
29 ADENIYI JONES AVENUE,
IKEJA, LAGOS, NIGERIA

NAME OF MANUFACTURER:
EMCURE PHARMACEUTICALS LIMITED,
PLOT NO. P-1 & P-2, I.T.B.T PARK, PHASEII, M.I.D.C.,
HINDJWADI, PUNE - 411057, MAHASARASHTRA, INDIA

8.0 MARKETING AUTHORISATION NUMBER(S)

Shall be provided when available.

9.0 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Not Applicable

10.0 DATE OF REVISION OF THE TEXT

Not Applicable