1.3 Product Information

1.3.1 Summary of product characteristics (SmPC)

Summary of product characteristics of Lamivudine and Tenofovir disoproxil fumarate tablets 300/300 mg is enclosed overleaf.

Note to Reviewer:
Brand Name is not applicable in Nigeria

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TENOLAM*

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains lamivudine 300 mg and tenofovir disoproxil fumarate 300 mg equivalent to tenofovir disoproxil 245 mg or 136 mg of tenofovir

Each tablet also contains:
Lactose monohydrate 14 mg

For a full list of excipients see 6.1

3. PHARMACEUTICAL FORM

Tablets (film coated)

White to off-white, oval shaped, film-coated tablets debossed with 'RH80' on one side and plain on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TENOLAM is indicated in combination with other antiretroviral products for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and adolescents from 10 years of age and weighing at least 30 kg.

TENOLAM may be used in combination with other measures for pre-exposure exposure prophylaxis (PrEP) in adults and patients weighing at least 35 kg at substantial risk of HIV infection.

TENOLAM may be used for post exposure prophylaxis (PEP) in adults and patients weighing at least 30 kg with an exposure that has potential for HIV transmission.

Consideration should be given to official treatment guidelines for HIV-1 infection, by WHO: http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf?ua=1

4.2 Posology and method of administration

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

Posology:

Adult and adolescents:
The recommended dose of TENOLAM is one tablet, taken once daily.

Special populations

Children:
HIV-therapy: TENOLAM 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).

* Trade names are not prequalified by WHO. This is the national medicines regulatory agency's (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

PrEP: TENOLAM should not be used in children under 10 years of age and in patients weighing less than 35 kg due to insufficient data on safety and efficacy (see section 5.2).
PEP: TENOLAM should not be used in children under 10 years of age and in patients weighing less than 30 kg due to insufficient data on safety and efficacy (see section 5.2).

A 28-day prescription should be provided for PEP following initial risk assessment. PEP should be offered and initiated as early as possible in all individuals with an exposure that has the potential for HIV transmission, preferably within 72 hours.

Elderly:
TENOLAM should be administered with caution to elderly patients (see section 4.4).

Mild renal impairment (creatinine clearance 50-80 ml/minute):
Once daily dosing of TENOLAM is recommended in patients with mild renal impairment (see section 4.4).

Moderate renal impairment (creatinine clearance 30-49 ml/minute) and severe renal impairment (creatinine clearance < 30ml/minute):
TENOLAM should not be used for PrEP in HIV-1 uninfected individuals with estimated creatinine clearance below 60 ml/minute.
Therapy with TENOLAM should not be initiated in patients with moderate or severe renal impairment (estimated Glomerular Filtration Rate (eGFR) < 50 ml/min) (see sections 4.4 and 5.2).
TENOLAM is not recommended for use in patients with creatinine clearance < 50 ml/minute (see sections 4.4. and 5.2), as appropriate dose adjustments are not possible. For these patients, separate formulations of lamivudine and tenofovir disoproxil should be used.

Hepatic impairement:
No dose adjustment is required (see sections 4.4 and 5.2).

Discontinuation of therapy:
Where discontinuation of therapy of HIV-1 infection with one of the components of TENOLAM is indicated or where dose modification is necessary, separate preparations of lamivudine and tenofovir disoproxil should be used. If TENOLAM 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).

PrEP and PEP may be discontinued 28 days after the last potential exposure to HIV if people do not have continuing substantial risk for acquiring HIV.

Advice on missed dose:
If a dose of TENOLAM 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 with the next due dose. If the patient misses a dose of TENOLAM 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 TENOLAM, another tablet should be taken. There is no need to take an extra dose if vomiting occurs more than 1 hour after taking TENOLAM.

Method of administration:
It is recommended that TENOLAM be swallowed whole with water.

TENOLAM can be taken with food or between meals.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

General:

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

Renal impairment:
Lamivudine and tenofovir disoproxil are both eliminated by renal excretion. Thus, exposure to both compounds increases in patients with renal dysfunction. The long term safety of tenofovir disoproxil and lamivudine in mild renal impairment (creatinine clearance 50-80 ml/minute) has not been fully assessed. Therefore, in patients with renal impairment TENOLAM 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).

Pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP):
Comprehensive Management to Reduce the Risk of Acquiring HIV-1:
Lamivudine and tenofovir disoproxil should be used for PrEP and PEP only as part of a comprehensive prevention strategy that includes other prevention measures, such as safer sex practices, because PrEP or PEP is not always effective in preventing the acquisition of HIV-1 (see 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).

Only an individual who has been confirmed HIV-negative should use TENOLAM to reduce the risk of acquiring HIV-1. HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking only lamivudine and tenofovir disoproxil, because these do 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.

If clinical symptoms consistent with acute viral infection are present and recent (< 1 month) HIV-exposure is 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 lamivudine and tenofovir disoproxil for PrEP or PEP, 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 lamivudine and tenofovir disoproxil dosing schedule. The effectiveness of lamivudine and tenofovir disoproxil 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.

Co-administration of other medicinal products
TENOLAM should not be given with any other medicinal products containing tenofovir disoproxil or tenofovir alafenamide, adefovir dipivoxil, lamivudine or emtricitabine*.

Co-administration of tenofovir disoproxil and didanosine is not recommended, as this may increase the risk of didanosine-related adverse events (see section 4.5). Rare cases of pancreatitis and lactic acidosis, sometimes fatal, have been reported. Furthermore, co-administration of tenofovir disoproxil and didanosine at a dose of 400 mg daily has been associated with a significant decrease in CD4 cell count, possibly due to an intracellular interaction increasing phosphorylated (i.e. active) didanosine. A low dose of 250 mg didanosine co-administered with tenofovir disoproxil has been associated with reports of high rates of virological failure with several combinations for the treatment of HIV-1 infection.

The combination of lamivudine with cladribine is not recommended (see section 4.5).

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

Renal impairment
If the creatinine test is routinely available, use the estimated glomerular filtration rate at baseline before initiating tenofovir disoproxil regimens. Benefits and risks should be carefully weighted when initiating lamivudine/tenofovir disoproxil fumarate 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 tenofovir disoproxil-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 lamivudine/tenofovir disoproxil fumarate, renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations (see section 4.8, proximal tubulopathy).

Consideration should also be given to interrupting treatment with tenofovir disoproxil in 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 lamivudine/tenofovir disoproxil fumarate should also be considered in case of progressive decline of renal function when no other cause has been identified.

A careful benefit-risk assessment is needed when lamivudine/tenofovir disoproxil fumarate 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 lamivudine/tenofovir disoproxil fumarate 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.

* Based on a systematic review it is suggested that emtricitabine and lamivudine are pharmacologically equivalent, and hence clinically interchangeable for therapy of HIV infection. Limited data are also indicative of a similar pharmacological effect in PrEP. Therefore, herein reference is made also to data obtained with emtricitabine.

TENOLAM should be avoided with concurrent or recent use of a nephrotoxic medicinal product (aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2). If concomitant use of tenofovir disoproxil and nephrotoxic agents is unavoidable, renal function should be monitored weekly.

Cases of acute renal failure after initiation of high dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs) have been reported in patients treated with tenofovir disoproxil and with risk factors for renal dysfunction. If this medicinal product is co-administered with an NSAID, renal function should be monitored adequately.

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

Pre-exposure Prophylaxis (PrEP) and post-exposure prophylaxis (PEP)
Lamivudine and tenofovir disoproxil should not be used for PrEP or PEP 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 or PEP, potential causes should be evaluated and potential risks and benefits of continued use re-assessed.

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 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.

In HIV-1 infected adolescents 12 years of age and older, the mean rate of bone gain was less in the tenofovir disoproxil -treated group compared to the placebo group. Skeletal growth (height) appeared to be unaffected. Markers of bone turnover in tenofovir disoproxil-treated adolescents suggest increased bone turnover, consistent with the effects observed in adults. Due to the possible effects of tenofovir on bone metabolism, lamivudine/tenofovir disoproxil fumarate should only be used in adolescents under the age of 18 if the benefits are considered to exceed the risk (see also section 4.8).

Pre-exposure Prophylaxis (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 emtricitabine*/tenofovir disoproxil prophylaxis (n=247) vs. placebo (n=251).

Patients with HIV and hepatitis B or C virus co-infection

Patients with chronic hepatitis B or C treated with antiretroviral therapy are at increased risk of severe and potentially fatal hepatic adverse reactions. Physicians should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus

* Based on a systematic review it is suggested that emtricitabine and lamivudine are pharmacologically equivalent, and hence clinically interchangeable for therapy of HIV infection. Limited data are also indicative of a similar pharmacological effect in PrEP. Therefore, herein reference is made also to data obtained with emtricitabine.

(HBV). In case of concomitant antiviral therapy for hepatitis B or C, refer also to the Summary of Product Characteristics for these medicinal products.

Lamivudine and tenofovir have anti-HBV activity when used in antiretroviral combination therapy to control HIV infection (see section 5.1). The combination of tenofovir disoproxil fumarate 300 mg and lamivudine 300 mg has not been studied for the treatment of HBV, lamivudine/tenofovir disoproxil fumarate is not indicated for the treatment of chronic HBV infection.

Discontinuation of lamivudine/tenofovir disoproxil fumarate 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 lamivudine/tenofovir disoproxil fumarate should be closely monitored with both clinical and laboratory follow-up for at least six months after stopping treatment. If appropriate, resumption of hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

Use with certain hepatitis C virus antiviral agents

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

Liver disease

The safety and efficacy of lamivudine and tenofovir disoproxil 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.

Lactic acidosis

Lactic acidosis is a rare but severe, potentially life-threatening complication associated with nucleoside reverse transcriptase inhibitors (NRTI). Several other agents of this class are known to cause lactic acidosis. Preclinical and clinical data suggest that the risk of lactic acidosis, a class effect of nucleoside analogues, is very low for tenofovir disoproxil. However, this risk cannot be excluded, as tenofovir is structurally related to nucleoside analogues. Lactic acidosis may occur after a few to several months of NRTI treatment. Patients with hyperlactataemia may be asymptomatic, critically ill, or may have non-specific symptoms such as dyspnoea, fatigue, nausea, vomiting, diarrhoea and abdominal pain. Risk factors for NRTI-related lactic acidosis include female gender and obesity. Patients at increased risk should be closely monitored clinically. Screening for hyperlactataemia in asymptomatic patients treated with NRTIs, however, is not recommended. Symptomatic patients usually have levels > 5 mmol/l and require discontinuation of all NRTIs. Lactic acid levels > 10 mmol/l usually are a medical emergency.

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
Nucleoside and nucleotide 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* or postnatally to nucleoside analogues. The main adverse events reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactataemia, hyperlipasaemia). These events are often transitory. Some late-onset neurological disorders have been reported rarely (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.

Pancreatitis
Treatment with lamivudine/tenofovir disoproxil fumarate should be stopped immediately if clinical signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur (see section 4.8).

Opportunistic infections
Patients receiving antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection. Therefore patients should remain under close clinical observation by health care providers experienced in the treatment of HIV infection.

Immune Reactivation Syndrome
In HIV infected patients with pre-existing severe immune deficiency, typically in the first few weeks or months after initiation of combination ART, 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) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment

Osteonecrosis
Cases of osteonecrosis have been reported, particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy. 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
Elderly patients are more likely to have decreased renal function; therefore caution should be exercised when treating elderly patients with TENOLAM

Transmission
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.

Excipients
TENOLAM contains lactose. Patients with rare hereditary problems of galactose intolerance (e.g. galactosaemia, the Lapp lactase deficiency or glucose-glactose malabsorption) may experience symptoms of intolerance when using it.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

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

Interactions relevant to lamivudine:

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

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

A modest increase in C_{max} (28 %) was observed for zidovudine when administered with lamivudine, however overall exposure (AUC) is not significantly altered. Zidovudine has no effect on the pharmacokinetics of lamivudine (see section 5.2).

Due to similarities, TENOLAM should not be administered concomitantly with other cytidine analogues, such as emtricitabine*. Moreover, TENOLAM should not be taken with any other medicinal products containing lamivudine (see section 4.4).

In vitro lamivudine inhibits the intracellular phosphorylation of cladribine leading to a potential risk of cladribine loss of efficacy in case of combination in the clinical setting. Some clinical findings also support a possible interaction between lamivudine and cladribine. Therefore, the concomitant use of lamivudine with cladribine is not recommended (see section 4.4).

Interactions relevant to tenofovir

TENOLAM should not be administered concomitantly with other medicinal products containing tenofovir disoproxil or tenofovir alefenamide.

Didanosine: Co-administration of tenofovir disoproxil 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 tenofovir disoproxil with medicinal products that reduce renal function or compete for active tubular secretion via transport proteins hOAT 1, hOAT 3 or MRP 4 (e.g. cidofovir) may increase serum concentrations of tenofovir, or the co-administered medicinal products, or both.

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

Given that tacrolimus can affect renal function, close monitoring is recommended when it is co-administered with tenofovir disoproxil.

Tenofovir disoproxil should not be administered concomitantly with adefovir dipivoxil.

* Based on a systematic review it is suggested that emtricitabine and lamivudine are pharmacologically equivalent, and hence clinically interchangeable for therapy of HIV infection. Limited data are also indicative of a similar pharmacological effect in PrEP. Therefore, herein reference is made also to data obtained with emtricitabine.

Other interactions

Interactions between TENOLAM and other medicinal products, are listed below (increased exposure is indicated as "↑", decreased exposure as "↓", no change as "↔").

Table 1: Interactions between tenofovir disproxil and other medicinal products

Drugs by therapeutic area	**Interaction**	**Recommendations concerning co-administration of TENOLAM**
Antiretrovirals		
Nucleoside reverse transcriptase inhibitors		
Abacavir / tenofovir		Abacavir and TENOLAM should not be co-administered, as the additive effect of abacavir is expected to be limited or absent.
Emtricitabine		TENOLAM should not be coadministered, due to the similarity between emtricitabine and lamivudine, and consequently expected additive toxicity and no benefit in efficacy. (See section 4.4.).
Didanosine (400 mg q.d.) / tenofovir	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. Also 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 TENOLAM and didanosine is not recommended (see section 4.4).
Protease inhibitors		
Atazanavir (400 mg once daily)	Atazanavir: AUC: ↓ 25% C_{max}: ↓ 21% C_{min}: ↓ 40% Tenofovir: AUC: ↑ 24% C_{max}: ↑ 14% C_{min}: ↑ 22%	If atazanavir and TENOLAM are co-administered, the dose of atazanavir should be 300 mg once daily together with ritonavir 100 mg once daily ("ritonavir-boosting", see below).

Atazanavir/Ritonavir (300 mg/100 mg once daily)	Atazanavir: AUC: ↓ 25% (↓ 42 to ↓ 3) C_{max}: ↓ 28% (↓ 50 to ↑ 5) Cmin: ↓ 26% (↓ 46 to ↑ 10) Tenofovir: AUC: ↑ 37% C_{max}: ↑ 34% C_{min}: ↑ 29%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir adverse events, including renal disorders. Renal function should be closely monitored (see section 4.4).
Lopinavir/Ritonavir (400 mg/100 mg twice daily)	Lopinavir/ritonavir: No significant effect on lopinavir/ritonavir Tenofovir: AUC: ↑ 32% C_{max}: ↔ C_{min}: ↑ 51%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir adverse events, including renal disorders. Renal function should be closely monitored (see section 4.4).
Darunavir/Ritonavir (300 mg/100 mg twice daily)	Darunavir: No significant effect on darunavir/ritonavir Tenofovir: AUC: ↑ 22% C_{min}: ↑ 37%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir adverse events, including renal disorders. Renal function should be closely monitored (see section 4.4).
Antiretrovirals: NRTIs		
Didanosine (400 mg once daily)	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. Also didanosine at 250 mg co-administered with tenofovir in several different antiretroviral combination regimens has been associated with a high rate of virological failure. Coadministration of TENOLAM and didanosine is not recommended (see section 4.4).
Adefovir dipivoxil	AUC: ↔ C_{max}: ↔	TENOLAM should not be administered concurrently with adefovir dipivoxil (see section 4.4).

Entecavir (1 mg once daily)	AUC: ↔ C_{max}: ↔	No clinically significant pharmacokinetic interactions when TENOLAM is co-administered with entecavir
Hepatitis C virus antiviral agents		
Sofosbuvir/tenofovir disoproxil	Tenofovir ↑ C_{max} 1.25 (1.08, 1.45) ↔ AUC 0.98 (0.91, 1.05) ↔ C_{min} 0.99 (0.91, 1.07) Sofosbuvir ↓ C_{max} 0.81 (0.60, 1.10) ↔ AUC 0.94 (0.76, 1.16) C_{min} (NA) GS-331007 (predominant inactive metabolite of sofosbuvir) ↓ C_{max} 0.77 (0.70, 0.84) ↔ AUC 0.84 (0.76, 0.92) C_{min} (NA)	No dose adjustment of sofosbuvir or TENOLAM is required when sofosbuvir and TENOLAM are used concomitantly.
Ledipasvir (90 mg once daily) /sofosbuvir (400 mg once daily) / tenofovir disoproxil	Tenofovir ↑ C_{max} 1.79 (1.56, 2.04) ↑ AUC 1.98 (1.77, 2.23) ↑ C_{min} 2.63 (2.32, 2.97) Ledipasvir ↓ C_{max} 0.66 (0.59, 0.75) ↓ AUC 0.66 (0.59, 0.75) ↓ C_{min} 0.66 (0.57, 0.76) Sofosbuvir ↔ C_{max} 1.03 (0.87, 1.23) ↔ AUC 0.94 (0.81, 1.10) GS-331007 ↔ C_{max} 0.86 (0.76,	Monitor for tenofovir-associated adverse reactions in patients receiving ledipasvir/sofosbuvir concomitantly with TENOLAM.

	0.96) ↔ AUC 0.90 (0.83, 0.97) ↔ C_{min} 1.07 (1.02, 1.13)	
Daclatasvir/ tenofovir disoproxil	↔ Daclatasvir AUC: 1.10 (1.01, 1.21) C_{max}: 1.06 (0.98, 1.15) C_{min}: 1.15 (1.02, 1.30) ↔ Tenofovir AUC: 1.10 (1.05, 1.15) C_{max}: 0.95 (0.89, 1.02) C_{min}: 1.17 (1.10, 1.24)	No dose adjustment of. Daclatasvir TENOLAM is required.

Other medicinal products
There were no clinically significant pharmacokinetic interactions when TENOLAM is co-administered with indinavir, efavirenz, saquinavir (ritonavir-boosted), methadone, ribavirin, rifampicin, tacrolimus, or the hormonal contraceptive norgestimate/ethinylestradiol.

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

4.6 Fertility, pregnancy and breast-feeding

Pregnancy

Animal studies do not indicate direct or indirect harmful effects of tenofovir disoproxil on pregnancy, fetal development, parturition or postnatal development (see section 5.3). The safety of tenofovir in human pregnancy has not been fully established. However, 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).

No increased risk of birth defects has been reported for lamivudine (www.apregistry.com). The use of TENOLAM may be considered during pregnancy.

Breast-feeding

Lamivudine and tenofovir disoproxil are found in breast milk of breast-feeding mothers.
Current recommendations on HIV and breast-feeding (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

There are limited clinical data with respect to the effect of tenofovir disoproxil on fertility. Animal studies do not indicate harmful effects of tenofovir disoproxil on fertility.
Animal studies showed that lamivudine had no effect 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, dizziness may occur during treatment with TENOLAM. Patients should be instructed that if they

experience these symptoms they should avoid potentially hazardous tasks such as driving and operating machinery.

4.8 Undesirable effects

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

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

The adverse events considered at least possibly related to treatment with the components of TENOLAM are listed below by body system, organ class and frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1 in 10), common (1 in 100 to 1 in 10), uncommon (1 in 1000 to 1 in 100), rare (1 in 10 000 to 1 in 1000), very rare (≤ 1 in 10 000), and 'unknown' (frequency cannot be estimated from the available data).

Blood and lymphatic systems disorders:

Uncommon	neutropenia, anaemia (occasionally severe), thrombocytopenia
Very rare	pure red cell aplasia

Metabolism and nutrition disorders:

Very common	Hypophosphataemia
Uncommon	hypokalaemia
Rare	lactic acidosis

Nervous system disorders:

Very common	dizziness
Common	headache and insomnia
Very rare	peripheral neuropathy (paraesthesia)

Respiratory, thoracic and mediastinal disorders:

Common	cough, nasal symptoms
Very rare	Dyspnoea

Gastrointestinal disorders:

Very common	diarrhoea, nausea, vomiting
Common	abdominal pain/cramps, flatulence
Uncommon	pancreatitis
Rare	elevated serum amylases

Hepatobiliary disorders:

Common	Increased transaminases
Rare	hepatic steatosis, hepatitis

Skin and subcutaneous tissue disorders:

Very common	rash
Common	alopecia
Rare	angioedema

Musculoskeletal and connective tissue disorders:

Common	arthralgia, muscle disorder
Uncommon	rhabdomyolysis, muscular weakness
Rare	osteomalacia (manifested as bone pain and infrequently contributing to fractures), myopathy

Renal and urinary disorders:

Uncommon	Increased serum creatinine, proximal renal tubulopathy (including Fanconi syndrome)
Rare	acute renal failure, renal failure, acute tubular necrosis, nephritis (including acute interstitial nephritis), nephrogenic diabetes insipidus

General disorders and administration site disorders:

Very common	asthenia
Common	fatigue, malaise, fever

In HBV infected patients, exacerbations of hepatitis have occurred after discontinuation of HBV therapy (see section 4.4).

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hyper-triglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see section 4.4).

Pre-exposure prophylaxis

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 disoproxil fumarate 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[b]	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[a]	NR[a]
	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%)

* Based on a systematic review it is suggested that emtricitabine and lamivudine are pharmacologically equivalent, and hence clinically interchangeable for therapy of HIV infection. Limited data are also indicative of a similar pharmacological effect in PrEP. Therefore, herein reference is made also to data obtained with emtricitabine.

Neutrophils	1 (1000-1300/mm^3)	23 (2%)	25 (2%)	208 (13%)	13 (10%)
	2-4 (< 750 mm^3)	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 reveiving emtricitabine*/tenofovir disoproxil fumarate in the iPrEx trial. Grades 2-3 proteinuria and glycosuria occurred in less than 1% of subjects treated with emtricitabine*/tenofovir disoproxil fumarate in the iPrEx trial and PartnersPrEP trial.

Six subjects in the tenofovir-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 disoproxil 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 (BMD)
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 disoproxil fumarate group compared with the placebo group, which returned toward baseline after discontinuation of treatment. Thirteen percent of subjects receiving emtricitabine*/tenofovir disoproxil fumarate 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 disoproxil fumarate 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 toxicity
As TENOLAM may cause renal damage, monitoring of renal function is recommended (see sections 4.4 and 4.8). Proximal renal tubulopathy generally resolved or improved after tenofovir disoproxil discontinuation. However, in some patients, declines in creatinine clearance did not completely resolve despite tenofovir disoproxil discontinuation. Patients at risk of renal impairment (such as patients with baseline renal risk factors, advanced HIV disease, or patients receiving concomitant nephrotoxic medications) are at increased risk of experiencing incomplete recovery of renal function despite tenofovir disoproxil discontinuation (see section 4.4).

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 therapy in the absence of proximal renal tubulopathy.

Interaction with didanosine
Co-administration of tenofovir disoproxil 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.

* Based on a systematic review it is suggested that emtricitabine and lamivudine are pharmacologically equivalent, and hence clinically interchangeable for therapy of HIV infection. Limited data are also indicative of a similar pharmacological effect in PrEP. Therefore, herein reference is made also to data obtained with emtricitabine.

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

Immune Reactivation Syndrome
In HIV infected patients with severe immune deficiency at the time of initiation of CART, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease) 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 or lamivudine as single entities were consistent with those observed in clinical studies in adults.

Other special population(s)

Elderly
Lamivudine/tenofovir disoproxil has not been studied in patients over the age of 65. Elderly patients are more likely to have decreased renal function, therefore caution should be exercised when treating elderly patients with emtricitabine*/tenofovir disoproxil.

HIV/HBV or HCV co-infected patients
Limited data on patients co-infected with HIV/HBV or HIV/HCV indicate that the adverse reaction profile of emtricitabine* and tenofovir disoproxil in patients co-infected with HIV/HBV or HIV/HCV was similar to that observed in patients infected with HIV without co-infection. However, as would be expected, 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 was similar in individuals with and without hepatitis B/C infection.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care professionals are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

4.9 Overdose

If overdose occurs the patient must be monitored for evidence of toxicity (see sections 4.8 and 5.3), and standard supportive treatment applied as necessary. Tenofovir disoproxil can be removed by haemodialysis; the median haemodialysis clearance of tenofovir disoproxil is 134 ml/minute. The elimination of tenofovir disoproxil by peritoneal dialysis has not been studied. Because a negligible amount of lamivudine was removed via (4-hour) haemodialysis, continuous ambulatory peritoneal

* Based on a systematic review it is suggested that emtricitabine and lamivudine are pharmacologically equivalent, and hence clinically interchangeable for therapy of HIV infection. Limited data are also indicative of a similar pharmacological effect in PrEP. Therefore, herein reference is made also to data obtained with emtricitabine.

dialysis, and automated peritoneal dialysis, it is not known if continuous haemodialysis would be clinically beneficial in a lamivudine overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for treatment of HIV infections, combinations, ATC code: J05AR12

Mechanism of action and pharmacodynamic effects

Lamivudine, the negative enantiomer of 2'-deoxy-3'-thiacytidine, is a dideoxynucleoside analogue. Tenofovir disoproxil is converted *in vivo* to tenofovir, a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate.

Lamivudine and tenofovir are phosphorylated by cellular enzymes to form lamivudine triphosphate and tenofovir diphosphate, respectively. Lamivudine triphosphate and tenofovir diphosphate competitively inhibit HIV-1 reverse transcriptase, resulting in DNA chain termination. Both substances are active against HIV-1 and HIV-2, as well as against hepatitis B virus.

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. In addition, a K70E substitution in HIV-1 reverse transcriptase has been selected by tenofovir and results in low-level reduced susceptibility to tenofovir. Clinical studies in treatment-experienced patients have assessed the anti-HIV activity of tenofovir against strains of HIV-1 with thymidine analogue mutations (TAMs), which are not selected for by tenofovir. HIV strains which expressed 3 or more TAMs that included either the M41L or L210W mutation showed reduced response to tenofovir.

In many cases when a lamivudine-containing treatment regimen fails (though less often when the treatment regimen contains a ritonavir-boosted protease inhibitor), the M184V mutation will be selected for at an early stage. M184V causes high-level resistance to lamivudine (> 300-fold reduced susceptibility). Virus with M184V replicates less well than does wild-type virus. *In vitro* data suggest that continuation of lamivudine in an antiretroviral regimen despite the development of M184V might provide residual antiretroviral activity (likely through impaired viral fitness). The clinical relevance of these findings is not established. Therefore, maintaining lamivudine therapy despite emergence of M184V mutation should be considered only when the activity of the best available NRTI backbone is significantly compromised.

Cross-resistance conferred by the M184V mutation is limited within the nucleoside/nucleotide inhibitor class of antiretroviral agents. M184V confers full cross-resistance against emtricitabine[*]. Zidovudine and stavudine maintain their antiretroviral activity against lamivudine-resistant HIV-1. Abacavir maintains its antiretroviral activity against lamivudine-resistant HIV-1 harbouring only the M184V mutation. The M184V mutant shows a < 4-fold decrease in susceptibility to didanosine; the clinical significance of this is unknown.

Clinical results

When tenofovir and lamivudine were combined with efavirenz in treatment-naïve patients with HIV-1, the proportion of patients (ITT) with HIV-RNA < 50 copies/ml were 76.3% and 67.8% at 48 and 144 weeks, respectively.

[*]Based on a systematic review it is suggested that emtricitabine and lamivudine are pharmacologically equivalent, and hence clinically interchangeable for therapy of HIV infection. Limited data are also indicative of a similar pharmacological effect in PrEP. Therefore, herein reference is made also to data obtained with emtricitabine.

Pre-exposure Prophylaxis

In a primary prevention trial (iPrEX), designed to evaluate the safety and efficacy of once-daily oral tenofovir disoproxil-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 emtricitabine*/tenofovir disoproxil versus placebo, in preventing HIV-1 acquisition by the uninfected partner, the risk reduction for emtricitabine*/tenofovir disoproxil 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.

5.2 Pharmacokinetic Properties

Tenofovir disoproxil fumarate

Tenofovir disoproxil fumarate is a water-soluble ester prodrug, which is rapidly converted *in vivo* to tenofovir and formaldehyde. Tenofovir is converted intracellularly to tenofovir monophosphate and to the active component, tenofovir diphosphate.

Absorption and Bioavailability

Following oral administration of tenofovir disoproxil to HIV infected patients, tenofovir disoproxil is rapidly absorbed and converted to tenofovir.

The oral bioavailability of tenofovir from tenofovir disoproxil in fasted patients was approximately 25%. Administration of tenofovir disoproxil with a high fat meal enhanced the oral bioavailability, with an increase in tenofovir AUC by approximately 40% and C_{max} by approximately 14%. However, administration of tenofovir disoproxil with a light meal did not have a significant effect on the pharmacokinetics of tenofovir.

Following single dose administration of TENOLAM in healthy volunteers, the mean (± SD) tenofovir C_{max} value was 305 (± 71) ng/ml and the corresponding value for AUC was 2229 (± 585) ng·hour/ml. The mean (± SD) tenofovir t_{max} value was 1.07 (± 0.5) hours.

Distribution

Following intravenous administration the steady-state volume of distribution of tenofovir disoproxil was estimated to be approximately 800 ml/kg. After oral administration of tenofovir disoproxil fumarate, tenofovir is distributed to most tissues with the highest concentrations occurring in the kidney, liver and the intestinal contents (preclinical studies). *In vitro* protein binding of tenofovir disoproxil to plasma or serum protein was less than 0.7 and 7.2%, respectively, over the tenofovir disoproxil concentration range 0.01–25 µg/ml.

Biotransformation

In vitro studies have determined that neither tenofovir disoproxil fumarate nor tenofovir are substrates for the CYP450 enzymes. Moreover, at concentrations substantially higher (approximately 300-fold) than those observed in vivo, tenofovir did not inhibit in vitro drug metabolism mediated by any of the major human CYP450 isoforms involved in drug biotransformation (CYP3A4, CYP2D6, CYP2C9, CYP2E1, or CYP1A1/2). Tenofovir disoproxil fumarate at a concentration of 100 µmol/l had no effect on any of the CYP450 isoforms, except CYP1A1/2, where a small (6%) but statistically significant reduction in metabolism of CYP1A1/2 substrate was observed. Based on these data, it is unlikely that

clinically significant interactions involving tenofovir disoproxil fumarate and medicinal products metabolised by CYP450 would occur.

Elimination

Tenofovir disoproxil is primarily excreted by the kidney, both by filtration and an active tubular transport system with about 70-80% of the dose excreted unchanged in urine following intravenous administration. Total clearance has been estimated to be approximately 230 ml/hour/kg (approximately 300 ml/minute). Renal clearance has been estimated to be approximately 160 ml/hour/kg (approximately 210 ml/minute), which is in excess of the glomerular filtration rate. This indicates that active tubular secretion is an important part of the elimination of tenofovir. Following oral administration the terminal half-life of tenofovir is approximately 12 to 18 hours.

Studies have established the pathway of active tubular secretion of tenofovir disoproxil to be influx into proximal tubule cell by the human organic anion transporters (hOAT) 1 and 3 and efflux into the urine by the multidrug resistant protein 4 (MRP 4).

Linearity/non-linearity

The pharmacokinetics of tenofovir were independent of tenofovir disoproxil fumarate dose over the dose range 75 to 600 mg and were not affected by repeated dosing at any dose level.

Age, gender and ethnicity

Limited data on the pharmacokinetics of tenofovir in women indicate no major gender effect. Tenofovir disoproxil fumarate exposure achieved in adolescent patients receiving oral daily doses of tenofovir disoproxil fumarate 300 mg was similar to exposures achieved in adults receiving once-daily doses of tenofovir disoproxil fumarate 300 mg. Pharmacokinetic studies have not been performed with tenofovir DF 300mg in children < 12 years and in the elderly (over 65 years). Pharmacokinetics have not been specifically studied in different ethnic groups.

Renal impairment

Pharmacokinetic parameters of tenofovir disoproxil were determined following administration of a single dose of tenofovir disoproxil fumarate 300 mg to 40 non-HIV, non-HBV infected patients with varying degrees of renal impairment defined according to baseline creatinine clearance (CrCl) (normal renal function when CrCl > 80 ml/minute; mild with CrCl = 50–79 ml/minute; moderate with CrCl = 30-49 ml/minute and severe with CrCl = 10–29 ml/minute). Compared with patients with normal renal function, the mean (%CV) tenofovir exposure increased from 2185 (12%) ng·hour/ml in subjects with CrCl > 80 ml/minute to respectively 3064 (30%) ng·hour/ml, 6 009 (42%) ng·hour/ml and 15 985 (45%) ng·hour/ml in patients with mild, moderate and severe renal impairment. The dosing recommendations in patients with renal impairment, with increased dosing interval, are expected to result in higher peak plasma concentrations and lower C_{min} levels in patients with renal impairment compared with patients with normal renal function. The clinical implications of this are unknown.

In patients with end-stage renal disease (ESRD) (CrCl < 10 ml/min) requiring haemodialysis, between-dialysis tenofovir concentrations substantially increased over 48 hours achieving mean C_{max} of 1032 ng/ml and mean $AUC_{0\text{-}48hour}$ of 42 857 ng·hour/ml. It is recommended that the dosing interval for tenofovir disoproxil fumarate 300 mg is modified in patients with creatinine clearance < 50 ml/minute or in patients who already have ESRD and require dialysis (see section 4.2).

The pharmacokinetics of tenofovir disoproxil in non-haemodialysis patients with creatinine clearance < 10 ml/minute and in patients with ESRD managed by peritoneal or other forms of dialysis have not been studied.

Hepatic impairment

A single 300-mg dose of tenofovir disoproxil fumarate was administered to non-HIV, non-HBV infected patients with varying degrees of hepatic impairment defined according to Child-Pugh-Turcotte (CPT) classification. Tenofovir pharmacokinetic parameters were not substantially altered in subjects with hepatic impairment suggesting that no dose adjustment is required in these subjects. The mean (%CV) tenofovir C_{max} and $AUC_{0\text{-}\infty}$ values were 223 (34.8%) ng/ml and 2050 (50.8%) ng·hour/ml, respectively, in normal subjects compared with 289 (46.0%) ng/ml and

231 (43.5%) ng·hour/ml in subjects with moderate hepatic impairment, and 305 (24.8%) ng/ml and 2740 (44.0%) ng·hour/ml in subjects with severe hepatic impairment.

Intracellular pharmacokinetics

In non-proliferating human peripheral blood mononuclear cells (PBMCs) the half-life of tenofovir diphosphate was found to be approximately 50 hours, whereas the half-life in phytohaemagglutinin-stimulated PBMCs was found to be approximately 10 hours.

Lamivudine

Lamivudine is rapidly absorbed following oral administration. Bioavailability is between 80 and 85%.

Absorption and Bioavailability

Following single dose administration of TENOLAM in healthy volunteers, the mean (± SD) lamivudine C_{max} value was 3289 (± 952) ng/ml and the corresponding value for AUC was 14610 (± 3241) ng·hour/ml. The mean (± SD) lamivudine t_{max} value was 1.37 (± 0.73) hours.

Co-administration of lamivudine with food results in a delay of T_{max} and a lower C_{max} (decreased by 47%). However, the extent (based on the AUC) of lamivudine absorbed is not influenced.

Distribution

Intravenous studies with lamivudine showed that the mean apparent volume of distribution is 1.3 l/kg.

Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited binding to the major plasma protein albumin (< 36% serum albumin *in vitro*).

Metabolism

Metabolism of lamivudine is a minor route of elimination. Lamivudine is predominantly cleared unchanged by renal excretion. The likelihood of metabolic drug interactions with lamivudine is low due to the small extent of hepatic metabolism (5–10 %) and low plasma protein binding.

Elimination

The observed lamivudine half-life of elimination is 5 to 7 hours. The active moiety, intracellular lamivudine triphosphate, has a prolonged terminal half-life in the cell i.e., 16 to 19 hours. The mean systemic clearance of lamivudine is approximately 0.32 l/hour/kg, with predominantly renal clearance (> 70%), including tubular secretion through the organic cationic transport system.

Special populations

Renal impairment: Studies in patients with renal impairment show that lamivudine elimination is affected by renal dysfunction. Dose reduction is recommended for patients with creatinine clearance ≤ 50 ml/minute (see section 4.2).

Hepatic impairment

No substantial alterations in the pharmacokinetics of lamivudine and tenofovir disoproxil was observed in subjects with variable degrees of hepatic impairment (see section 4.2).

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

Tenofovir

Preclinical studies in rats, dogs and monkeys revealed target-organ effects on 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. However, no conclusion could be drawn on the mechanism(s) underlying these toxicities.

Reproductive studies were conducted in rats and rabbits. There were no effects on mating or fertility parameters or on any pregnancy or fetal parameter. There were no gross fetal alterations of soft or skeletal tissues. Tenofovir disoproxil reduced the viability index and weight of pups in peri-post-natal toxicity studies.

Genotoxicity studies have shown that tenofovir disoproxil was negative in the *in vivo* mouse bone marrow micronucleus assay but was positive for inducing forward mutations in the *in vitro* L5178Y mouse lymphoma cell assay in the presence or absence of S9 metabolic activation. Tenofovir disoproxil was positive in the Ames test (strain TA 1535) in two out of three studies, once in the presence of S9 mix (6.2- to 6.8-fold increase) and once without S9 mix. Tenofovir disoproxil was also weakly positive in an *in vivo*/*in vitro* unscheduled DNA synthesis test in primary rat hepatocytes.

Tenofovir disoproxil 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 concentration of tenofovir disoproxil 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.

Lamivudine

Administration of lamivudine in animal toxicity studies at high doses was not associated with any major organ toxicity. At the highest dosage levels, minor effects on indicators of liver and kidney function were reported together with occasional reductions in liver weight. The clinically relevant effects noted were reduction in red blood cell count and neutropenia.

Lamivudine was not mutagenic in bacterial tests, but showed activity in an *in vitro* cytogenetic assay and the mouse lymphoma assay. Lamivudine was not genotoxic *in vitro* at doses that gave plasma concentrations around 40–50 times higher than the expected clinical plasma levels. As the *in vitro* mutagenic activity of lamivudine could not be confirmed *in vivo*, it is concluded that lamivudine should not represent a genotoxic hazard to patients undergoing treatment.

The results of long-term carcinogenicity studies in rats and mice did not show any carcinogenic potential relevant for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet:

Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate

Film coat:

Hypromellose
Lactose monohydrate
Titanium dioxide
Triacetin

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30° C. Protect from moisture.

6.5 Nature and contents of container

White, opaque 100 cc HDPE bottle with white polypropylene, round cylindrical 38 mm child-resistant cap with heat-seal liner. The bottle also contains a silica gel desiccant sachet.
Do not remove the silica gel desiccant sachet.
Pack size: 30 tablets.

White, opaque 200 cc HDPE bottle with white polypropylene, round cylindrical 38 mm child-resistant cap with heat-seal liner. The bottle also contains a silica gel desiccant sachet.
Do not remove the silica gel desiccant sachet.
Pack size: 90 tablets.

6.6 Instructions for use and handling and disposal

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. SUPPLIER

Sun Pharmaceutical Industries Limited
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8. WHO REFERENCE NUMBER (PREQUALIFICATION PROGRAMME)

HA525

9. DATE OF FIRST PREQUALIFICATION

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10. DATE OF REVISION OF THE TEXT

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Section 6 updated in June 2018
Section 6 updated in June 2019.

Detailed information on this medicine is available on the World Health Organization (WHO) web site: https://extranet.who.int/prequal

References

General reference sources for this SmPC include:

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