SUMMARY OF PRODUCT CHARACTERISTICS

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1. NAME OF THE MEDICINAL PRODUCT

Tenofovir disoproxil fumarate tablets 300 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

Tenofovir Disoproxil Fumarate 300 mg (equivalent to tenofovir disoproxil 245 mg).

This medicinal product contains lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Blue colored, oval shaped, film-coated tablets, with "LA16" debossed on one side and plain on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

HIV-1 infection: Tenolaurus 300mg Tablets is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in patients weighing 30 kg or more.

The choice of Tenolaurus 300mg Tablets to treat antiretroviral-experienced patients with HIV-1 infection should be based on individual viral resistance testing or the treatment history of the patient.

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

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

For use of antiretroviral agents for post-exposure prophylaxis consult the most recent official guidelines, e.g. those by WHO.

Hepatitis B infection: Tenolaurus 300mg Tablets is indicated for the treatment of chronic hepatitis B in adults with:

• compensated liver disease and evidence of immune active disease, i.e. active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation or fibrosis.

• evidence of lamivudine-resistant hepatitis B virus.

• decompensated liver disease.

Tenolaurus 300mg Tablets is indicated for the treatment of chronic hepatitis B in adolescents 12 to 18 years of age and weighing at least 35 kg with:

• compensated liver disease and evidence of immune active disease, i.e. active viral replication, persistently elevated serum ALT levels and histological evidence of active inflammation or fibrosis.

Consideration should be given to official treatment guidelines for chronic hepatitis B (e.g. issued by WHO).

4.2 Posology and method of administration

Therapy should be initiated by a health care provider experienced in the management of HIV infection or treatment of chronic hepatitis B.

Posology

The recommended dose for the treatment or prevention of HIV as well as for the treatment of chronic hepatitis B is one tablet of Tenolaurus 300mg Tablets once daily taken orally with food or between meals.

The optimal duration of treatment for chronic hepatitis B is unknown. Treatment discontinuation may be considered as follows:

In patients who are positive for hepatitis B e antigen (HBeAg-positive patients) without cirrhosis, treatment should be continued

- for at least 6-12 months after confirmed BeAG seroconversion (i.e. HBeAg loss and Hepatitis B Virus (HBV) DNA loss with d detection of antibodies against HBeAG) or
- until Hepatitis B surface antigen (HBsAG) seroconversion or
- until loss of efficacy (see section 4.4).

Serum ALT and HBV DNA levels should be followed regularly after treatment discontinuation to detect any late virological relapse.

In HBeAg negative patients without cirrhosis treatment should be continued

- at least until HBs seroconversion or
- until there is evidence of loss of efficacy.

With prolonged treatment longer than 2 years, regular reassessment is recommended to confirm that the therapy remains appropriate for the patient.

If treatment with Tenolaurus 300mg Tablets is discontinued in patients with chronic hepatitis B (with or without HIV co-infection), the patient should be closely monitored for evidence of exacerbation of hepatitis (see section 4.4).

Children and adolescents

HIV-therapy: Tenolaurus 300mg Tablets should not be used in patients weighing less than 30 kg since appropriate dose adjustments cannot be achieved with this product (see section 5.2). For patients weighing less than 30 kg other formulations with lower amounts of the active substance are available.
The safety and efficacy of tenofovir disoproxil in HIV-1 infected children under 2 years of age have not been established. No data are available.
PrEP: Tenolaurus 300mg Tablets should not be used in adolescents weighing less than 35 kg due to insufficient data on safety and efficacy (see section 5.2).
Hepatitis B: The safety and efficacy of tenofovir disoproxil in children with chronic hepatitis B aged less than 12 years or weighing less than 35 kg have not been established. No data are available.
Elderly:
There is no need for dose adjustment of Tenolaurus 300mg Tablets in the elderly, except in renal impairment (see sections 4.4 and 5.2).

Renal impairment:
Tenofovir is eliminated by renal excretion and the exposure to tenofovir increases in patients with renal dysfunction. Patients with renal impairment may require close monitoring of renal function (see section 4.4).
Mild renal impairment: The long-term safety of tenofovir in mild renal impairment (creatinine clearance 50- 80 ml/minute) has not been fully assessed. Therefore, in patients with renal impairment Tenolaurus 300mg Tablets should only be used if the potential benefits of treatment are considered to outweigh the potential risks. No dose adjustment is necessary for patients with mild renal impairment (creatinine clearance 50–80 ml/minute). Routine monitoring of calculated creatinine clearance and serum phosphate should be performed in patients with mild renal impairment (see section 4.4).
Moderate renal impairment (creatinine clearance 30-49 ml/minute):
Tenolaurus 300mg Tablets should not be used for PrEP in HIV-1 uninfected individuals with estimated creatinine clearance below 60 ml/minute.
For HIV-therapy, administration of Tenolaurus 300mg Tablets every 48 hours is recommended, based on modelling of single-dose pharmacokinetic data for tenofovir disoproxil in non-HIV infected subjects with varying degrees of renal impairment (see section 4.4). These dose adjustments have not been confirmed in clinical studies and the clinical response to treatment should be closely monitored in such patients (see sections 4.4 and 5.2).
Severe renal impairment (creatinine clearance < 30 ml/minute) and haemodialysis patients:
For patients with no alternative treatment available, Tenolaurus 300mg Tablets may be used with prolonged dose intervals as follows:
Severe renal impairment: Tenolaurus 300mg Tablets administered every 72-96 hours (dosing twice a week).

Haemodialysis patients: Tenolaurus 300mg Tablets administered after a haemodialysis session every 7 days (assuming three haemodialysis sessions per week, each of approximately 4 hours duration or after 12 hours cumulative haemodialysis).

No dosing recommendations can be given for non-haemodialysis patients with creatinine clearance less than 10 ml/minute.

Children: The use of tenofovir disoproxil is not recommended in paediatric patients with renal impairment.

Hepatic impairment

No dose adjustment is required for tenofovir disoproxil in patients with hepatic impairment (see sections 4.4 and 5.2).

Missed dose

If a patient misses a dose of Tenolaurus 300mg Tablets within 12 hours of the time it is usually taken, the patient should take the medicine as soon as possible and resume the normal dosing schedule with the next due dose. If a patient misses a dose of Tenolaurus 300mg Tablets by more than 12 hours and it is almost time for the next dose, the patient should not take the missed dose and simply resume the usual dosing schedule.

If the patient vomits within 1 hour of taking Tenolaurus 300mg Tablets, another tablet should be taken. There is no need to take an extra dose if the patient vomits more than 1 hour after taking Tenolaurus 300mg Tablets.

Method of administration

Tenolaurus 300mg Tablets should be swallowed whole. It can be taken with food or between meals.

A granules formulation of tenofovir disoproxil may be available for patients who cannot swallow tablets. If granules are not available, the tablets may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately.

4.3 Contraindications

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

4.4 Special warnings and special precautions for use

General

HIV antibody testing should be offered to all HBV infected patients before initiating tenofovir therapy (see below *Co-infection with HIV-1 and hepatitis B*). In turn, HBV antibody testing should be offered to all individuals before initiating tenofovir therapy.

Pre-exposure prophylaxis

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

Tenolaurus 300mg Tablets should be used for pre-exposure prophylaxis only as part of a comprehensive prevention strategy that includes other prevention measures, such as safer sex practices,

because pre- exposure prophylaxis 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 Tenolaurus 300mg Tablets to prevent acquiring HIV-1 infection. Use of tenofovir disoproxil alone in an individual with undetected HIV-1 infection can lead to the virus developing resistance to the drug. Individuals with HIV-1 infection must be treated with a combination of antiretrovirals.

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

If the patient has symptoms consistent with acute viral infection, and exposure to such an infection within the previous month is suspected, the start of PrEP should be delayed for at least one month. HIV-1 status should be then reconfirmed using a reliable test.

While using tenofovir disoproxil for PrEP, HIV-1 screening tests should be repeated at least every 3 months. If symptoms consistent with acute HIV-1 infection develop following a potential exposure event, PrEP should be discontinued until negative infection status is confirmed using a reliable test for diagnosing HIV-1.

Uninfected individuals should be counselled to strictly adhere to the recommended Tenolaurus 300mg Tablets dosing schedule. The effectiveness of tenofovir disoproxil in reducing the risk of acquiring HIV-1 correlates strongly with adherence as demonstrated by drug levels in clinical trials.

The risk for HIV-1 acquisition should be assessed at each visit.

Preliminary data for a combination of tenofovir disoproxil and emtricitabine indicate that the time before PrEP with tenofovir disoproxil is fully effective may be up to seven days for anal sex and up to three weeks for vaginal sex. Individuals who wish to discontinue PrEP should be advised to continue taking tenofovir disoproxil for at least 4 weeks after the last potential HIV exposure.

Virus transmission:

HIV-1: While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk may remain. Precautions to prevent transmission should be taken in accordance with national guidelines.

Chronic hepatitis B: Patients must be advised that tenofovir disoproxil has not been proven to prevent transmission of HBV to others through sexual contact or contamination with blood. Precautions to avoid transmission must continue to be used.

Co-administration of other medicinal products

Tenolaurus 300mg Tablets should not be administered with any other medicinal products containing tenofovir disoproxil, tenofovir alafenamide or adefovir dipivoxil.

Co-administration of tenofovir disoproxil and didanosine is not recommended because the risk of didanosine-related adverse events may increase (see section 4.5). Rare cases of pancreatitis and lactic acidosis, sometimes fatal, have been reported. Co-administration of tenofovir disoproxil and didanosine 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 lower dose of 250 mg didanosine administered with tenofovir disoproxil therapy has been associated with high rates of virological failure with several combinations for the treatment of HIV-1 infection.

Triple therapy with nucleosides/nucleotides: There have been reports of a high rate of virological failure and of early emergence of resistance in HIV patients when tenofovir disoproxil was combined with lamivudine and abacavir as well as with lamivudine and didanosine.

Renal effects

Tenofovir is primarily excreted by the kidneys. Renal toxicity, including renal failure and Fanconi syndrome has been reported with the use of tenofovir disoproxil in clinical practice (see section 4.8). It is recommended that creatinine clearance or estimated glomerular filtration rate be calculated in all individuals prior to initiating therapy and as clinically appropriate during therapy with Tenolaurus 300mg Tablets.

Renal safety with tenofovir disoproxil has been studied only to a very limited degree in adult patients with impaired renal function (creatinine clearance less than 80 ml/minute). Therefore, tenofovir disoproxil should be used only if the potential benefits of treatment are considered to outweigh the potential risks. Tenofovir disoproxil is not recommended in patients with severe renal impairment (creatinine clearance less than 30 ml/minute) and in patients who require haemodialysis. However, if no alternative treatment is available, the dosing interval of tenofovir disoproxil must be adjusted and renal function should be closely monitored (see sections 4.2 and 5.2).

Pre-exposure Prophylaxis

Tenolaurus 300mg Tablets should not be used for PrEP in individuals with an estimated creatinine clearance below 60 ml/minute. Creatinine clearance should be measured every 3 months during the first 12 months and annually thereafter. If the estimated creatinine clearance decreases in individuals using this medicine for PrEP, potential causes should be evaluated and potential risks and benefits of continued use re-assessed.

HIV-therapy

If the creatinine test is routinely available, the estimated glomerular filtration rate should be established before starting treatment with tenofovir disoproxil.

Benefits and risks should be carefully weighted when initiating tenofovir disoproxil in patients with an estimated glomerular filtration rate less than 50 ml/minute, or in long-term diabetes, uncontrolled hypertension and renal failure.

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 use of boosted protease inhibitors or nephrotoxic drugs) to detect and limit progression of renal impairment. If available, serum phosphate should also be measured in these patients.

If serum phosphate in adults is less than 15 mg/l (0.48 mmol/l), in children less than 30 mg/l (0.96 mmol/l) or creatinine clearance is decreased to less than 50 ml/minute in any patient receiving Tenolaurus 300mg Tablets, renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations (see section 4.8, proximal tubulopathy).

Consideration should also be given to interrupting treatment with tenofovir disoproxil in patients with creatinine clearance decreased to less than 50 ml/minute or decreases in serum phosphate below 10 mg/l (0.32 mmol/l). Interrupting treatment with Tenolaurus 300mg Tablets should also be considered in case of progressive decline of renal function when no other cause has been identified.

Dose interval adjustment is recommended for patients with creatinine clearance less than 50 ml/minute (see section 4.2). However, limited clinical study suggest that prolonging the dose interval is not optimal and could result in increased toxicity and possibly inadequate response

Use of tenofovir disoproxil should be avoided with concurrent use of a nephrotoxic medicine (e.g. high-dose or multiple non-steroidal anti-inflammatory drugs, aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2). If concomitant use of tenofovir disoproxil and nephrotoxic agents is unavoidable, renal function should be monitored weekly (see section 4.5).

Bone effects

In a controlled clinical study in adults comparing tenofovir disoproxil and stavudine (each in combination with lamivudine and efavirenz), bone mineral density of the spine decreased and bone biomarkers changed from baseline in both treatment groups, but the changes were significantly greater in the tenofovir disoproxil group at 144 weeks. Decreases in bone mineral density of the hip were significantly greater in this group until 96 weeks. However, over 144 weeks, the risk of fractures wa not increased and there was no evidence of clinically relevant bone abnormalities.

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.

Renal and bone effects in adolescent and paediatric population:

There are uncertainties associated with the long-term effects of bone and renal toxicity. Moreover, it is not known if toxicity is reversible. Therefore, a multidisciplinary approach is recommended to adequately weigh up the balance between benefit and risk of treatment on a case-by-case basis, decide

on the appropriate monitoring during treatment (including decision for treatment withdrawal) and consider the need for supplementation.

Tenofovir disoproxil is not recommended in paediatric patients with renal impairment.

If renal abnormalities are suspected or detected during therapy with tenofovir disoproxil then a nephrologist should be consulted to consider interruption of tenofovir disoproxil treatment. Interrupting treatment with tenofovir disoproxil should also be considered in case of progressive decline of renal function when no other cause has been identified.

The effects of tenofovir disoproxil-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, an endocrinologist, or a nephrologist, or both should be consulted.

Osteonecrosis: Cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease or long-term exposure to combination antiretroviral therapy. The aetiology 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 have joint pain, joint stiffness or difficulty in movement.

Liver disease

Safety and efficacy data are very limited in liver transplant patients. The safety of tenofovir in patients with decompensated liver disease and who have a Child-Pugh-Turcotte score over 9 has not been thoroughly evaluated. These patients may be at higher risk of serious hepatic or renal adverse reactions. Therefore, hepatobiliary and renal parameters should be closely monitored in these patients.

Exacerbations of hepatitis

Flares on treatment: Spontaneous exacerbations of chronic hepatitis B are relatively common and are characterised by transient increases in serum ALT. After initiating antiviral therapy, serum ALT may increase in some patients as serum HBV DNA levels decline (see section 4.8). Among tenofovir-treated patients, exacerbations typically occurred after 4-8 weeks of therapy. In patients with compensated liver disease, these increases in serum ALT are generally not accompanied by an increase in serum bilirubin concentrations or hepatic decompensation. Patients with cirrhosis may be at a higher risk for hepatic decompensation following hepatitis exacerbation, and therefore should be monitored closely during therapy.

Flares after treatment discontinuation*:* Acute exacerbation of hepatitis has been reported in patients who have discontinued hepatitis B therapy. Post-treatment exacerbations are usually associated with rising HBV DNA, and the majority appears to be self-limited. However, severe exacerbations, including fatalities, have been reported. Hepatic function should be monitored at repeated intervals with both clinical and laboratory follow-up for at least 6 months after discontinuation of hepatitis B therapy. If appropriate, hepatitis B therapy may be resumed. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended because post-treatment exacerbation of hepatitis may

lead to hepatic decompensation. Liver flares are especially serious, and sometimes fatal, in patients with decompensated liver disease.

Co-infection with hepatitis C or D

There are no data on the efficacy of tenofovir in patients co-infected with hepatitis C or D virus.

Co-infection with HIV-1 and hepatitis B

Due to the risk of development of HIV resistance, tenofovir disoproxil should be used only as part of an appropriate antiretroviral combination regimen in HIV and HBV co-infected patients. Patients with liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered. However, it should be noted that increases of ALT can be part of HBV clearance during therapy with tenofovir (see above, Flares on treatment').

Use with certain hepatitis C virus antiviral agents

Co-administration of tenofovir disoproxil with ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir has been shown to increase plasma concentrations of tenofovir, especially when used together with an HIV regimen containing tenofovir disoproxil and a pharmacokinetic enhancer (e.g. ritonavir). The safety of tenofovir disoproxil in the setting of ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir and a pharmacokinetic enhancer has not been established. The potential risks and benefits associated with co-administration of ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir 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, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir concomitantly with tenofovir disoproxil and a boosted HIV protease inhibitor should be monitored for adverse reactions related to tenofovir disoproxil.

Weight and metabolism

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 lifestyle. 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.

Established HIV treatment guidelines should be consulted on monitoring blood lipids and glucose. Lipid disorders should be managed as clinically appropriate.

Mitochondrial dysfunction

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

neurological disorders are transient or permanent is currently unknown. Any child exposed *in utero* to nucleoside and nucleotide analogues, even HIV-negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. These findings do not affect national recommendations on antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Immune Reactivation Syndrome

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

Autoimmune disorders (such as Graves' disease) have also been reported 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 HIV treatment.

Elderly

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

Excipients

Tenofovir 300 mg Tablets contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption may experience symptoms of intolerance.

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

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 pathway of tenofovir, the potential for CYP450-mediated interactions involving tenofovir with other medicinal products is low.

<u>Concomitant use not recommended</u>

Tenolaurus 300mg Tablets should not be administered with any other medicines containing:

- tenofovir disoproxil
- tenofovir alafenamide
- adefovir dipivoxil
- didanosine (see section 4.4 and Table 2)

Renally eliminated medicinal products

Since tenofovir is primarily eliminated by the kidneys, co-administration of tenofovir disoproxil fumarate with medicinal products that reduce renal function or compete for active tubular secretion via transport proteins hOAT 1, hOAT 3 or MRP 4 (e.g. cidofovir) may increase serum concentrations of tenofovir and/or the co-administered medicines, or both.

Nephrotoxic medicinal products:

Use of tenofovir disoproxil should be avoided with concurrent use of a nephrotoxic medicinal product. Examples include, but are not limited to high-dose or multiple non-steroidal anti-inflammatory drugs, aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir and 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.

Other interactions:

Interactions between tenofovir disoproxil and HIV protease inhibitors, as well as antiviral agents other than protease inhibitors, are listed in the table below (increased exposure is indicated as "↑", decreased exposure as "↓", no change as "↔",).

Interactions between tenofovir disoproxil fumarate and other medicinal products

Medicinal product by therapeutic areas (dose in mg)	**Effects on drug levels Mean % change in AUC, C_{max}, C_{min}**	**Recommendation on co-administration with tenofovir disoproxil 245 mg**
ANTI-INFECTIVES		
Antiretrovirals		
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 tenofovir are co-administered, atazanavir should be given at a dose 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% C_{max}: ↓ 28%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir-associated

	C_{min}: ↓ 26% Tenofovir: AUC: ↑ 37% C_{max}: ↑ 34% C_{min}: ↑ 29%	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 pharmacokinetics parameters. Tenofovir: AUC: ↑ 32% C_{max}: ↔ C_{min}: ↑ 51%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir-associated adverse events, including renal disorders. Renal function should be closely monitored (see section 4.4).
Darunavir/Ritonavir (300 mg/100 mg twice daily)	Darunavir: No significant effect on darunavir/ritonavir pharmacokinetics parameters. Tenofovir: AUC: ↑ 22% C_{min}: ↑ 37%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir-associated adverse events, including renal disorders. Renal function should be closely monitored (see section 4.4).
NRTIs		
Didanosine	Didanosine AUC ↑ 40-60%	The risk of didanosine-related adverse effects (e.g. pancreatitis, lactic acidosis) appear to be increased, and CD4 cells may decrease significantly on co-administration. Also didanosine at 250 mg co-administered with tenofovir with several different antiretroviral combination regimens has been associated with a high rate of virological failure. Co-administration of tenofovir disoproxil and didanosine is not recommended (see section 4.4).

Adefovir dipivoxil	AUC: ↔ C_{max}: ↔	Tenofovir disoproxil fumarate should not be administered concurrently with adefovir dipivoxil (see section 4.4).
Entecavir	AUC: ↔ C_{max}: ↔	No clinically significant pharmacokinetic interactions when tenofovir disoproxil fumarate was co-administered with entecavir.
Hepatitis C virus antiviral agents		
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Atazanavir/Ritonavir (300 mg q.d./100 mg q.d.) + Emtricitabine/Tenofovir disoproxil fumarate (200 mg/245 mg q.d.)[1]	Ledipasvir: AUC: ↑ 96% C_{max}: ↑ 68% C_{min}: ↑ 118% Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 42% Atazanavir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 63% Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 45% Emtricitabine: AUC: ↔ C_{max}: ↔	Increased plasma concentrations of tenofovir resulting from coadministration of tenofovir disoproxil fumarate, ledipasvir/sofosbuvir and atazanavir/ritonavir may increase adverse reactions related to tenofovir disoproxil fumarate, including renal disorders. The safety of tenofovir disoproxil fumarate when used with ledipasvir/sofosbuvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring, if other alternatives are not available (see section 4.4).

	C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↑ 47% C_{min}: ↑ 47%	
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Darunavir/Ritonavir (800 mg q.d./100 mg q.d.) + Emtricitabine/Tenofovir disoproxil fumarate (200 mg/245 mg q.d.)[1]	Ledipasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Sofosbuvir: AUC: ↓ 27% C_{max}: ↓ 37% GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Darunavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 48% Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 50%	Increased plasma concentrations of tenofovir resulting from coadministration of tenofovir disoproxil fumarate, ledipasvir/sofosbuvir and darunavir/ritonavir may increase adverse reactions related to tenofovir disoproxil fumarate, including renal disorders. The safety of tenofovir disoproxil fumarate when used with ledipasvir/sofosbuvir and a pharmacokinetic enhancer (e.g. ritonavir) has not been established. The combination should be used with caution with frequent renal monitoring, if other alternatives are not available (see section 4.4).

	C_{max}: ↑ 64% C_{min}: ↑ 59%	
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate (600 mg/200 mg/245 mg q.d.)	Ledipasvir: AUC: ↓ 34% C_{max}: ↓ 34% C_{min}: ↓ 34% Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 98% C_{max}: ↑ 79% C_{min}: ↑ 163%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil fumarate, including renal disorders. Renal function should be closely monitored (see section 4.4).
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Emtricitabine/Rilpivirine/Tenofovir disoproxil fumarate (200 mg/25 mg/245 mg q.d.)	Ledipasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Sofosbuvir: AUC: ↔	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil fumarate,

	C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Rilpivirine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 40% C_{max}: ↔ C_{min}: ↑ 91%	including renal disorders. Renal function should be closely monitored (see section 4.4).
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Dolutegravir (50 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Ledipasvir: AUC: ↔ Cmax: ↔ Cmin: ↔ Dolutegravir AUC: ↔	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil fumarate, including renal disorders. Renal function should be closely monitored (see section 4.4).

	Cmax: ↔ Cmin: ↔ Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↑ 65% C_{max}: ↑ 61% C_{min}: ↑ 115%	
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Atazanavir/Ritonavir (300 mg q.d/100 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 42% Velpatasvir: AUC: ↑ 142% Cmax: ↑ 55% Cmin: ↑ 301% Atazanavir: AUC: ↔ Cmax: ↔ Cmin: ↑ 39% Ritonavir: AUC: ↔ Cmax: ↔ Cmin: ↑ 29%	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, sofosbuvir/velpatasvir and atazanavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with sofosbuvir/velpatasvir and a pharmacokinetic enhancer (e.g. ritonavir) has not been established. The combination should be used with caution with frequent renal monitoring (see section 4.4).

	Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↑ 55% C_{min}: ↑ 39%	
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Darunavir/Ritonavir (800 mg q.d./100 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↓28% Cmax: ↓ 38% GS-331007[2]: AUC: ↔ Cmax: ↔ Cmin: ↔ Velpatasvir: AUC: ↔ Cmax: ↓ 24% Cmin: ↔ Darunavir: AUC: ↔ Cmax: ↔ Cmin: ↔ Ritonavir: AUC: ↔ Cmax: ↔ Cmin: ↔ Emtricitabine: AUC: ↔ Cmax: ↔	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, sofosbuvir/velpatasvir and darunavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with sofosbuvir/velpatasvir and a pharmacokinetic enhancer (e.g. ritonavir) has not been established. The combination should be used with caution with frequent renal monitoring (see section 4.4).

	Cmin: ↔ Tenofovir: AUC: ↑ 39% Cmax: ↑ 55% Cmin: ↑ 52%	
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Lopinavir/Ritonavir (800 mg/200 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↓29% Cmax: ↓ 41% GS-331007[2]: AUC: ↔ Cmax: ↔ Cmin: ↔ Velpatasvir: AUC: ↔ Cmax: ↓ 30% Cmin: ↑ 63% Lopinavir: AUC: ↔ Cmax: ↔ Cmin: ↔ Ritonavir: AUC: ↔ Cmax: ↔ Cmin: ↔ Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↔	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, sofosbuvir/velpatasvir and lopinavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with sofosbuvir/velpatasvir and a pharmacokinetic enhancer (e.g. ritonavir) has not been established. The combination should be used with caution with frequent renal monitoring (see section 4.4).

	Cmax: ↑ 42%	
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Raltegravir (400 mg b.i.d) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ Cmax: ↔ GS-331007[2]: AUC: ↔ Cmax: ↔ Cmin: ↔ Velpatasvir: AUC: ↔ Cmax: ↔ Cmin: ↔ Raltegravir: AUC: ↔ Cmax: ↔ Cmin: ↓ 21% Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↑ 40% Cmax: ↑ 46% Cmin: ↑ 70%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4).
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Efavirenz/Emtricitabine/Tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ Cmax: ↑ 38% GS-331007[2]: AUC: ↔	Concomitant administration of sofosbuvir/velpatasvir and efavirenz is expected to decrease plasma concentrations of velpatasvir. Co-administration of sofosbuvir/velpatasvir with

	Cmax: ↔ Cmin: ↔ Velpatasvir: AUC: ↓ 53% Cmax: ↓ 47% Cmin: ↓ 57% Efavirenz: AUC: ↔ Cmax: ↔ Cmin: ↔ Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↑ 81% Cmax: ↑ 77% Cmin: ↑ 121%	efavirenz-containing regimens is not recommended.
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Emtricitabine/Rilpivirine/Tenofovir disoproxil (200 mg/25 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ Cmax: ↔ GS-331007[2]: AUC: ↔ Cmax: ↔ Cmin: ↔ Velpatasvir: AUC: ↔ Cmax: ↔ Cmin: ↔ Emtricitabine:	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4).

	AUC: ↔ Cmax: ↔ Cmin: ↔ Rilpivirine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↑ 40% Cmax: ↑ 44% Cmin: ↑ 84%	
Sofosbuvir/Velpatasvir/ Voxilaprevir (400 mg/100 mg/ 100 mg+100 mg q.d.)3 + Darunavir (800 mg q.d.) + Ritonavir (100 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ Cmax: ↓ 30% Cmin: N/A GS-331007[2]: AUC: ↔ Cmax:↔ Cmin: N/A Velpatasvir: AUC: ↔ Cmax: ↔ Cmin: ↔ Voxilaprevir: AUC: ↑ 143% Cmax:↑ 72% Cmin: ↑ 300% Darunavir: AUC: ↔ Cmax: ↔ Cmin: ↓ 34%	Increased plasma concentrations of tenofovir resulting from coadministration of tenofovir disoproxil, sofosbuvir/velpatasvir/voxilaprevir and darunavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with sofosbuvir/velpatasvir/voxilaprevir and a pharmacokinetic enhancer (e.g. ritonavir) has not been established. The combination should be used with caution with frequent renal monitoring (see section 4.4)

	Ritonavir: AUC: ↑ 45% Cmax: ↑ 60% Cmin: ↔ Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↑ 39% Cmax: ↑ 48% Cmin: ↑ 47%	
Sofosbuvir (400 mg q.d.) + Efavirenz/Emtricitabine/Tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ Cmax: ↓ 19% GS-331007[2]: AUC: ↔ Cmax: ↓ 23% Efavirenz: AUC: ↔ Cmax: ↔ Cmin: ↔ Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↔ Cmax: ↑ 25% Cmin: ↔	No dose adjustment is required.

[1] Data generated from simultaneous dosing with ledipasvir/sofosbuvir. Staggered administration (12 hours apart) provided similar results.

2 The predominant circulating metabolite of sofosbuvir.

3 Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

Studies conducted with other medicinal products

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

Food effect

Food enhances the bioavailability of tenofovir (see section 5.2). Tenofovir disoproxil can be taken with food or between meals.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

A large amount of data on pregnant women (more than 1,000 pregnancy outcomes) indicate no malformations or foetal/neonatal toxicity associated with tenofovir disoproxil. Animal studies do not indicate reproductive toxicity (see section 5.3). No increase in birth defects was seen (www.apregistry.com). The use of tenofovir disoproxil may be considered during pregnancy, if necessary

Breast-feeding

Tenofovir is present in human milk. There is insufficient information on the effects of tenofovir in breast- feeding infants. Current recommendations on HIV/HBV/PrEP and breastfeeding (e.g. those from the WHO) should be consulted before advising women 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.

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, users should be informed that dizziness has been reported during treatment with tenofovir disoproxil.

4.8 Undesirable effects

HIV-1 and hepatitis B: 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 tenofovir disoproxil (see section 4.4).
HIV-1: Approximately one third of patients are expected to experience adverse reactions following treatment with tenofovir disoproxil in combination with other antiretroviral agents. These reactions are usually mild to moderate gastrointestinal events. Approximately 1% of tenofovir disoproxil-treated patients discontinued treatment due to the gastrointestinal events. Co-administration of tenofovir and didanosine is not recommended as this increase adverse reactions (see section 4.5). Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported (see section 4.4).
Hepatitis B: Approximately one quarter of patients can be expected to experience adverse reactions following treatment with tenofovir disoproxil, most of which are mild. In clinical trials of HBV infected patients, the most frequently occurring adverse reaction to tenofovir disoproxil was nausea (5.4%). Acute exacerbation of hepatitis has been reported in patients on treatment as well as in patients who have discontinued hepatitis B therapy (see section 4.4).
HIV-1 clinical studies: Assessment of adverse reactions from HIV-1 clinical study data is based on experience in two studies in 653 treatment-experienced patients receiving treatment with tenofovir disoproxil (n = 443) or placebo (n = 210) in combination with other antiretroviral medicinal products for 24 weeks and also in a double-blind comparative controlled study in which 600 treatment-naïve patients received treatment with tenofovir disoproxil 245 mg (n = 299) or stavudine (n = 301) in combination with lamivudine and efavirenz for 144 weeks.
Hepatitis B clinical studies: Assessment of adverse reactions from HBV clinical study data is primarily based on experience in two double-blind comparative controlled studies in which 641 adult patients with chronic hepatitis B and compensated liver disease received treatment with tenofovir disoproxil 245 mg daily (n = 426) or adefovir dipivoxil 10 mg daily (n = 215) for 48 weeks. The adverse reactions observed with continued treatment for 384 weeks were consistent with the established pattern of tenofovir disoproxil adverse effects.
Patients with decompensated liver disease: The safety profile of tenofovir disoproxil in patients with decompensated liver disease was assessed in a double-blind active controlled study in which adult patients received treatment with tenofovir disoproxil (n = 45) or emtricitabine plus tenofovir disoproxil (n = 45) or entecavir (n = 22) for 48 weeks.
In the tenofovir disoproxil treatment arm, 7% of patients discontinued treatment due to an adverse event; 9% of patients experienced a confirmed increase in serum creatinine of at least 0.5 mg/dl or confirmed

serum phosphate of less than 2 mg/l through week 48. At 168 weeks 13% of the tenofovir disoproxil group experienced an increase in serum creatinine of at least 0.5 mg/dl or confirmed serum phosphate of less than 2 mg/dl.

At week 168, the rate of death was of 13% and was comparable to the other treatment groups (tenofovir disoproxil/emtricitabine or entecavir). Hepatocellular carcinoma occurred in 18% with tenofovir disoproxil (compared with 7% in the tenofovir disoproxil /emtricitabine and 9% in the entecavir group).

Subjects with a high baseline Child-Pugh-Turcotte score were at higher risk of developing serious adverse events (see section 4.4).

Patients with lamivudine-resistant chronic hepatitis B: No new adverse reactions to tenofovir disoproxil were identified from a randomised, double-blind study in which 280 lamivudine-resistant patients received treatment with tenofovir disoproxil (n = 141) or emtricitabine/tenofovir disoproxil (n = 139) for 240 weeks.

The adverse reactions with at least a possible relationship to treatment are listed below by body system organ class and absolute frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10) or common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) or rare (≥ 1/10,000 to < 1/1,000).

The following adverse reactions were associated with tenofovir disoproxil based on clinical study and post- marketing experience.

Metabolism and nutrition disorders:

Very common: hypophosphataemia[1]

Uncommon: hypokalaemia[1]

Rare: lactic acidosis

Nervous system disorders:

Very common: dizziness

Common: headache

Gastrointestinal disorders:

Very common: diarrhoea, vomiting, nausea

Common: abdominal pain, abdominal distension, flatulence

Uncommon: pancreatitis

Hepatobiliary disorders:

Common: increased transaminases

Rare:	hepatic steatosis, hepatitis
Skin and subcutaneous tissue disorders:	
Very common:	rash
Rare:	angioedema
Musculoskeletal and connective tissue disorders:	
Uncommon:	rhabdomyolysis[1], muscular weakness[1]
Rare:	osteomalacia (manifested as bone pain and infrequently contributing to fractures)[1, 2], myopathy[1]
Renal and urinary disorders:	
Uncommon:	increased creatinine
Rare:	acute renal failure, renal failure, acute tubular necrosis, proximal renal tubulopathy (including Fanconi syndrome), nephritis (including acute interstitial nephritis)[2], nephrogenic diabetes insipidus
General disorders and administration site conditions:	
Very common:	asthenia
Common:	fatigue

[1] This adverse reaction may occur as a consequence of proximal renal tubulopathy. It is not considered to be causally associated with tenofovir disoproxil in the absence of this condition.

[2] This adverse reaction was identified through post-marketing surveillance.

Pre-exposure prophylaxis

In three published, randomised controlled HIV-prevention trials in men who have sex with men, heterosexual serodiscordant couples and injecting drug users, in which 2989 uninfected adults received tenofovir disoproxil 300 mg tablets no new adverse reactions were reported. In individual studies the following adverse events were reported more frequently in the treatment group as compared to placebo. Their relationship to study drug is unknown.

Abdominal pain (up to 12% in the first month, lower thereafter) Nausea (up to 10%)

Diarrhoea (up to 4% in the first month, lower thereafter)

Fatigue (up to 10% in the first month, lower thereafter)

Depression (up to 9%)

Dizziness (up to 6%) Syphilis (2% vs. 1%)

Urethritis (1.64% vs. 1.26%)

Soft tissue injury (2 vs. 1%)

Back pain (up to 11%)

Decreased bone density (6% vs. 4%)

Bone fracture (8% vs. 6%)

The following laboratory abnormalities were reported in these trials (tenofovir disoproxil vs. placebo): neutropenia grade 1/2 (15% vs. 13%), decreased haemoglobin (7% vs. 5%), decreased phophorus grade 1 (16% vs. 14%), AST elevations grade 1/2 (2% to 1%), ALT elevations grade 1/2 (2 vs.1), elevations in ALT/AST were reported much more frequently in the study with injecting drug users; however, the difference to placebo was not larger.

Creatinine abnormalities occurred at similar rates on tenofovir disoproxil and placebo.

Description of selected adverse reactions

HIV-1 and hepatitis B

Renal impairment

As tenofovir disoproxil may cause renal damage, monitoring of renal function is recommended (see sections 4.4). 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 incomplete recovery of renal function despite tenofovir disoproxil discontinuation (see section 4.4).

HIV-1

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 antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease) have also been reported (see section 4.4).

Osteonecrosis

Cases of osteonecrosis have been reported. The frequency of this is unknown (see section 4.4).

Hepatitis B

Exacerbations of hepatitis during treatment

In studies with nucleoside-naïve patients, on-treatment ALT elevations > 10 times ULN (upper limit of normal) and > 2 times baseline occurred in 2.6% of tenofovir disoproxil-treated patients. Most cases were associated with a ≥ 2 log10 copies/ml reduction in viral load that preceded or coincided with the ALT elevation. Periodic monitoring of hepatic function is recommended during treatment (see section 4.4).

Exacerbations of hepatitis after discontinuation of treatment

In HBV-infected patients, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of HBV therapy (see section 4.4).

Paediatric population

HIV-1 therapy

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

Reductions in bone mineral density (BMD) have been reported in paediatric patients. In HIV-infected adolescents, the BMD Z-scores in subjects who received tenofovir disoproxil were lower than those in subjects who received placebo. In HIV-infected children, the BMD Z-scores in subjects who switched to tenofovir disoproxil were lower than those in subjects who remained on regimens containing stavudine or zidovudine (see sections 4.4 and 5.1).

In one study, 4 out of 89 paediatric patients treated with tenofovir disoproxil (median tenofovir disoproxil treatment 312 weeks) discontinued due to adverse reactions consistent with proximal renal tubulopathy. Seven patients had estimated glomerular filtration rate (GFR) values between 70 and 90 mL/minute/1.73 m2. Among them, two patients had a clinically meaningful decline in estimated GFR which improved after discontinuation of tenofovir disoproxil.

Pre-exposure prophylaxis

Tenofovir is not indicated for PrEP in children. No safety data are available in adolescents.

Chronic hepatitis B

The adverse reactions in adolescent patients who received treatment with tenofovir disoproxil were consistent with those in clinical studies of tenofovir disoproxil in adults.

Bone mineral density (BMD) declined in HBV infected adolescents. The BMD Z-scores in subjects who received tenofovir disoproxil were lower than those in subjects who received placebo (see sections 4.4 and 5.1).

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via EFDA yellow Card Scheme, online at https://primaryreporting.who-umc.org/ET or toll free call 8482 to Ethiopian food and drug authority (EFDA).

4.9 Overdose

Symptoms

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.

Management

Tenofovir can be removed by haemodialysis; the median haemodialysis clearance of tenofovir is 134 ml/min. It is not known whether tenofovir can be removed by peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nucleoside and nucleotide reverse transcriptase inhibitors, ATC code: J05AF07

Mechanism of action: Tenofovir disoproxil fumarate is the fumarate salt of the prodrug tenofovir disoproxil. Tenofovir disoproxil is absorbed and converted to the active substance tenofovir, which is a nucleoside monophosphate (nucleotide) analogue. Tenofovir is then converted to the active metabolite, tenofovir diphosphate, an obligate chain terminator, by constitutively expressed cellular enzymes. Tenofovir diphosphate inhibits HIV-1 reverse transcriptase and the HBV polymerase by direct binding competition with the natural deoxyribonucleotide substrate and, after incorporation into DNA, by DNA chain termination.

Tenofovir diphosphate is a weak inhibitor of cellular polymerases α, β, and γ. At concentrations of up to 300 μmol/l, tenofovir has also shown no effect on the synthesis of mitochondrial DNA or the production of lactic acid in in vitro assays.

Data pertaining to HIV

HIV antiviral activity in vitro*:* Tenofovir is active against HIV-1 subtypes A, C, D, E, F, G, and O and against HIVBaL in primary monocyte/macrophage cells. Tenofovir shows activity *in vitro* against HIV-2, with an EC50 of 4.9 μmol/l in MT-4 cells.

Resistance: The K65R mutation is selected in vitro when HIV-1 is cultured in the presence of increasing tenofovir concentrations. It may also emerge in vivo upon virological failure of a treatment regimen including tenofovir. K65R reduces tenofovir susceptibility in vitro approximately 2-fold, and has been associated with a lack of response to tenofovir-containing regimens. Clinical studies in treatment-experienced patients have assessed the anti-HIV activity of tenofovir against strains of HIV-1 with thymidine analogue mutations (TAMs), which are not selected for by tenofovir. Patients whose HIV expressed 3 or more TAMs that included either the M41L or L210W mutation showed reduced response to tenofovir disoproxil.

Clinical efficacy and safety

HIV-1 therapy

In treatment-experienced adult patients the time-weighted average change from baseline in log10 plasma HIV-1 RNA levels the time-weighted average change from baseline in log10 plasma HIV-1 RNA levels (DAVG24) at week 24 was -0.03 log10 copies/ml and -0.61 log10 copies/ml for the placebo and tenofovir disoproxil 245 mg recipients ($p < 0.0001$). The antiviral response was durable with DAVG at week 48 being -0.57 log10 copies/ml, the proportion of patients with HIV-1 RNA below 400 or 50 copies/ml was 41% and 18% respectively.

In treatment-naïve adult patients the proportion of patients with HIV-1 RNA below 400 copies/ml and 50 copies/ml at 48 weeks of treatment was 80% and 76% respectively in the tenofovir disoproxil 245 mg arm, compared to 84% and 80% in the stavudine arm. At 144 weeks, the proportion of patients with HIV-1 RNA below 400 copies/ml and 50 copies/ml was 71% and 68% respectively in the tenofovir disoproxil arm, compared to 64% and 63% in the stavudine arm.

A consistent response to treatment with tenofovir disoproxil 245 mg was seen regardless of baseline HIV-1 RNA and CD4 count.

Pre-exposure Prophylaxis

In a randomized, double-blind study with 400 men who have sex with men (USA), randomized to tenofovir disoproxil 245 mg or placebo, 7 HIV-seroconversions were reported after a study duration of 24 months.

None occurred among participants taking tenofovir disoproxil.

In a randomized, double blind study with HIV-1 serodiscordant heterosexual couples (Kenya, Uganda) 1584 HIV-negative partners received tenofovir disoproxil and 1584 received placebo for a median of 23 months. Seventeen HIV-infections occurred in the tenofovir disoproxil and 52 in the placebo group, indicating a relative reduction of 67% in the incidence of HIV in the tenofovir disoproxil group (ITT analysis, 95% CI 44 to 81%, $p < 0.001$).

In total, 2413 injecting drug users were randomized to receive either tenofovir disoproxil 245 mg or placebo in a double-blind fashion (Thailand). After a mean follow-up of 4 years, 17 HIV infections were confirmed in the tenofovir disoproxil group versus 35 in the placebo group (ITT-analysis), indicating a 51.8% reduction in HIV incidence (95% CI 15.3 to 73.7%, $p = 0.01$).

Data pertaining to HBV

Resistance: No HBV mutations associated with tenofovir disoproxil resistance have been identified.

Clinical efficacy and safety

The demonstration of benefit of tenofovir disoproxil in compensated and decompensated disease is based on virological, biochemical and serological responses in adults with HBeAg-positive and HBeAg-negative chronic hepatitis B. Treated patients included those who were treatment-naïve, lamivudine-experienced, adefovir dipivoxil-experienced and patients with lamivudine or adefovir dipivoxil resistance mutations at baseline. Benefit has also been demonstrated based on histological responses in compensated patients.

Results through 48 weeks from two randomised, phase 3 double-blind studies comparing tenofovir disoproxil to adefovir dipivoxil in adult patients with compensated liver disease in 266 HBeAg-positive patients and in 375 patients negative for HBeAg and positive for HBeAb.

In both of these studies tenofovir disoproxil was associated with significantly greater proportions of patients with HBV DNA < 400 copies/ml and < 29 IU/ml (limit of quantification of the assay), when compared to adefovir dipivoxil 10 mg treatment. Both treatments produced similar results with regard to histological response (defined as Knodell necroinflammatory score improvement of at least 2 points without worsening in Knodell fibrosis) at week 48.

In HBeAg-negative patients a significantly greater proportion of patients in the tenofovir disoproxil group than in the adefovir had normalized ALT and achieved ABsAg loss at week 48.

Response to treatment with tenofovir disoproxil was comparable in nucleoside-experienced and nucleoside- naïve patients and in patients with normal ALT and abnormal ALT at baseline.

Roll-over to open-label tenofovir disoproxil showed that viral suppression, biochemical and serological responses were maintained with continued tenofovir disoproxil treatment through the study to 384 weeks.

Parameter	**HBeAg negativ**		**HBeAg positive**	
	Tenofovir disoproxil fumarate 245 mg n = 250	Adefovir dipivoxil 10 mg n = 125	Tenofovir disoproxil fumarate 245 mg n = 176	Adefovir dipivoxil 10 mg n = 90
Histological response (%)[a] week 48	72	69	74	68
HBV DNA (%) < 400 copies/ml (< 69 IU/ml)	93*	63	76*	13
HBV DNA (%) < 169 copies/ml (< 29 IU/ml) Week 48	91*	56	69*	9
Histological response a,b (%) Week 240	88 [130/148]	85 [63/74]	90 [63/70]	92 [36/39]

* p-value *versus* adefovir dipivoxil < 0.05.

a Knodell necroinflammatory score improvement of at least 2 points without worsening in Knodell fibrosis score.

b 48 weeks double-blind TDF or adefovir dipivoxil followed by up to 192 weeks open-label TDF.

In a randomised, 48-week double-blind, controlled study of tenofovir disoproxil 245 mg in adult patients co- infected with HIV-1 and chronic hepatitis B with prior lamivudine experience treatment with tenofovir disoproxil was associated with a mean change in serum HBV DNA from baseline, in the patients for whom there was 48-week data, of -5.74 log10 copies/ml (n = 18). In addition, 61% of patients had normal ALT at week 48.

The efficacy and safety of tenofovir disoproxil 245 mg or tenofovir disoproxil 245 mg plus 200 mg emtricitabine has been evaluated in a randomised, double-blind study, in HBeAg-positive and HBeAg-negative adult patients who had persistent viraemia (HBV DNA ≥ 1000 copies/ml) while receiving adefovir dipivoxil 10 mg for more than 24 weeks. Overall at week 24, treatment with tenofovir disoproxil resulted in 66% (35/53) of patients with HBV DNA < 400 copies/ml (< 69 IU/ml) versus 69% (36/52) of patients treated with emtricitabine/tenofovir disoproxil (p = 0.672). In addition 55% (29/53) of patients treated with tenofovir disoproxil had undetectable HBV DNA (< 169 copies/ml [< 29 IU/ml]; the limit of quantification of the assay) versus 60% (31/52) of patients treated with emtricitabine/tenofovir disoproxil (p =0.504). Long- term studies to evaluate the benefit/risk of bitherapy with emtricitabine /tenofovir disoproxil in HBV monoinfected patients are ongoing.

A randomized (2:2:1), double-blind, active controlled study evaluated the safety and efficacy of tenofovir disoproxil, emtricitabine/tenofovir disoproxil and entecavir in 102 patients with decompensated liver disease. In patients with Child-Pugh-Turcotte scores ≤ 9, 74% (29/39) of tenofovir disoproxil, and 94% (33/35) of emtricitabine/tenofovir disoproxil treatment groups achieved HBV DNA < copies/ml after 48 weeks of treatment.

Using a noncompleter/switch = failure analysis, 50% (21/42) of subjects receiving tenofovir disoproxil, 76% (28/37) of subjects receiving emtricitabine/tenofovir disoproxil and 52% (11/21) of subjects receiving entecavir achieved HBV DNA < 400 copies/ml at week 168.

HBeAg-positive and HBeAg-negative patients with lamivudine-resistant HBV and compensated liver disease (n=280) were studied in a randomised, double-blind study. After 240 weeks of treatment, 117 of 141 subjects (83%) randomised to tenofovir disoproxil had HBV DNA < 400 copies/ml, and 51 of 79 subjects (65%) had ALT normalisation. After 240 weeks of treatment with emtricitabine plus tenofovir disoproxil, 115 of 139 subjects (83%) had HBV DNA < 400 copies/ml, and 59 of 83 subjects (71%) had ALT normalisation.

Among the HBeAg positive subjects randomised to tenofovir disoproxil, 16 of 65 subjects (25%) experienced HBeAg loss, and 8 of 65 subjects (12%) experienced anti-HBe seroconversion through week

240. In the HBeAg positive subjects randomised to emtricitabine plus tenofovir disoproxil, 13 of 68 subjects (19%) experienced HBeAg loss, and 7 of 68 subjects (10%) experienced anti-HBe seroconversion through week 240.

Clinical resistance

In 821 adult and 52 paediatric patients with CHB from the above studies evaluations for genotypic resistance showed that no mutations associated with tenofovir disoproxil resistance have developed.

Paediatric and adolescent population

HIV-1: HIV-1 infected treatment-experienced patients aged 12 to up to 18 years were treated with tenofovir disoproxil (n = 45) or placebo (n = 42) in combination with an optimized background regimen for 48 weeks. Due to limitations of the study, a benefit of tenofovir disoproxil over placebo was not demonstrated based on plasma HIV-1 RNA levels at week 24. However, a benefit is expected for the adolescent population based on extrapolation of adult data and comparative pharmacokinetic data (see section 5.2).

In this study, patients who received treatment with tenofovir disoproxil or placebo, mean changes in lumbar spine bone mineral density (BMD) Z-score at week 48 were -0.215 and -0.165, and were -0.254 and -0.179 in total body BMD Z-score for the tenofovir disoproxil and placebo groups, respectively. At week 48, six adolescents in the tenofovir disoproxil group and one adolescent in the placebo group had significant lumbar spine BMD loss (defined as > 4% loss). Among 28 patients receiving 96 weeks of treatment tenofovir disoproxil, BMD Z-scores declined by -0.341 for lumbar spine and -0.458 for total body.

In a second study with 97 treatment-experienced patients aged 2 to up to 12 years with stable virologic suppression on stavudine- or zidovudine-containing regimens were randomised to either replace stavudine or zidovudine with tenofovir disoproxil (n = 48) or continue on their original regimen (n = 49) for 48 weeks. At week 48, 83% of patients in the tenofovir disoproxil group and 92% of patients in the stavudine or zidovudine group had HIV-1 RNA concentrations < 400 copies/ml. When missing data were excluded, 91% of patients in the tenofovir disoproxil group and 94% of patients in the stavudine or zidovudine treatment group had HIV-1 RNA concentrations < 400 copies/ml at week 48.

In this second study, patients who received treatment with tenofovir disoproxil, or stavudine or zidovudine, mean changes in lumbar spine BMD Z-score at week 48 were 0.032 and 0.087, and were -0.184 and -0.027 in total body BMD Z-score for the tenofovir disoproxil and stavudine or zidovudine groups, respectively. One subject treated with tenofovir disoproxil and no subject treated with stavudine or zidovudine had significant (> 4%) lumbar spine BMD loss at week 48. BMD Z-scores declined by -0.012 for lumbar spine and by -0.338 for total body in the 64 subjects who were treated with tenofovir disoproxil for 96 weeks.

BMD Z-scores were not adjusted for height and weight.

In this study, 4 out of 89 paediatric patients exposed to tenofovir disoproxil discontinued due to adverse reactions consistent with proximal renal tubulopathy (median TDF exposure 104 weeks).

Chronic hepatitis B: HBeAg-negative and HBeAg-positive patients aged 12 to up to 18 years with chronic HBV were treated with tenofovir disoproxil 245 mg or placebo. At week 72, overall 88% (46/52) of patients in the tenofovir disoproxil group and 0% (0/54) of patients in the placebo group had

HBV DNA < 400 copies/ml. ALT normalizsation at week 72 occurred in 74% of patients in the tenofovir disoproxil group and in 31% in the placebo group. Response to treatment with tenofovir disoproxil was comparable in nucleoside- naïve and nucleos(t)ide-experienced patients, including lamivudine-resistant patients. At week 72, 96% of immune-active patients (HBV DNA ≥ 105 copies/ml, serum ALT > 1.5 times upper limit of normal) in the tenofovir disoproxil group and 0% (0/32) of patients in the placebo group had HBV DNA < 400 copies/ml.

After 72 weeks of blinded randomized treatment, each subject could switch to open-label tenofovir disoproxil treatment up to week 192. After week 72, virologic suppression was maintained for those receiving double-blind tenofovir disoproxil followed by open-label tenofovir disoproxil (tenofovir disoproxil-tenofovir disoproxil group): 86.5% (45/52) of subjects in the tenofovir disoproxil-tenofovir disoproxil group had HBV DNA < 400 copies/ml at week 192. Among the subjects who received placebo during the double-blind period, the proportion of subjects with HBV DNA < 400 copies/mL rose sharply after they began treatment with open-label tenofovir disoproxil (PLB- tenofovir disoproxil group): 74.1% (40/54) of subjects in the PLB-tenofovir disoproxil group had HBV DNA< 400 copies/ml at week 192.

The proportion of subjects with ALT normalization at week 192 in the tenofovir disoproxil-tenofovir disoproxil group was 75.8% (25/33) among those who were HBeAg positive at baseline and 100.0% (2 of 2 subjects) among those who were HBeAg negative at baseline. Similar percentages of subjects in the tenofovir disoproxil-tenofovir disoproxil and PLB-tenofovir disoproxil groups (37.5% and 41.7%, respectively) experienced seroconversion to anti-HBe through week 192.

Bone Mineral Density data are summarised in the table below.

	Baseline		**Week 72**		**Week 192**	
	Tenofovir disoproxil-tenfovir disoproxil	**PLB-tenofovir disoproxil**	**Tenofovir disoproxil-tenfovir disoproxil**	**PLB-tenofovir disoproxil**	**Tenofovir disoproxil-tenfovir disoproxil**	**PLB-tenofovir disoproxil**
Lumbar spine mean (SD) BMD Z-score[a]	−0.42 (0.762)	-0.26 (0.806)	-0.49 (0.852)	-0.23 (0.893)	-0.37 (0.946)	-0.44 (0.920)

Lumbar spine mean (SD) change from baseline BMD Z-score[a]	NA	NA	-0.06 (0.320)	0.10 (0.378)	0.02 (0.548)	-0.10 (0.543)
Whole body mean (SD) BMD Z-score[a]	−0.19 (1.110)	−0.23 (0.859)	−0.36 (1.077)	−0.12 (0.916)	−0.38 (0.934)	−0.42 (0.942)
Whole body mean (SD) change from baseline BMD Z-score[a]	NA	NA	−0.16 (0.355)	0.09 (0.349)	-0.16 (0.521)	-0.19 (0.504)
Lumbar spine BMD at least 6% decrease[b]	NA	NA	1.9% (1 subject)	0%	3.8% (2 subjects)	3.7 % (2 subjects)
Whole body BMD at least 6% decrease[b]	NA	NA	0%	0%	0%	1.9% (1 subjects)
Lumbar spine BMD mean % increase	NA	NA	5.14%	8.08%	10.05%	11.21%
Whole body BMD mean % increase	NA	NA	3.07%	5.39%	6.09%	7.22%

NA = Not Applicable

a BMD Z-scores not adjusted for height and weight

b Primary safety endpoint through week 72

5.2 Pharmacokinetic properties

<table>
<tr><td></td><td>Tenofovir disoproxil</td></tr>
<tr><td>General</td><td></td></tr>
<tr><td></td><td>Tenofovir disoproxil is a water-soluble ester prodrug, which is rapidly converted in vivo to tenofovir. Tenofovir is converted intracellularly to tenofovir monophosphate and to the active component, tenofovir diphosphate.</td></tr>
<tr><td>Absorption</td><td></td></tr>
<tr><td>Absolute bioavailability</td><td>NA</td></tr>
<tr><td>Oral bioavailability</td><td>25%</td></tr>
<tr><td>Food effect</td><td>
<table>
<tr><td></td><td>AUC(0-∞)</td><td>Cmax</td><td>Tmax</td></tr>
<tr><td>Light meal</td><td>No Significant effect</td><td>No Significant effect</td><td>No Significant effect</td></tr>
<tr><td>High fat</td><td>40% ↑</td><td>14% ↑</td><td>2 h</td></tr>
</table>
</td></tr>
<tr><td>Distribution</td><td></td></tr>
<tr><td>Volume of distribution (mean)</td><td>800 ml/kg</td></tr>
<tr><td>Plasma protein binding in vitro</td><td>< 0.7 % (serum protein binding < 7.2%)</td></tr>
</table>

Tissue distribution	Well distributed, with highest concentrations in kidney and liver.
Metabolism	
	In vitro studies have determined that neither tenofovir disoproxil nor tenofovir is a substrate for the CYP450 enzymes.
Active metabolite(s)	Tenofovir
Elimination	
Elimination half life	Tenofovir: 12 to 18 h Tenofovir diphosphate: 10h in intracellular activated resting peripheral blood mononuclear cells and 50 hours in resting peripheral blood mononuclear cells.
Mean systemic clearance (Cl/F)	0.23 L/h/kg
% of dose excreted in urine	70-80% as unchanged drug
% of dose excreted in faeces	NA
Pharmacokinetic linearity	Linear pharmacokinetics (dose range 75 to 600 mg)
Drug interactions *(in vitro*)	
Transporters	Substrate of hOAT 1, hOAT3 and MRP 4. .
Metabolizing enzymes	No significant inhibition of CYP3A4, CYP2D6, CYP2C9, CYP2E1, or CYP1A1/2

Age, gender and race

Pharmacokinetic studies have not been performed in the elderly (over 65 years).

Limited data on the pharmacokinetics of tenofovir in women indicate no major gender effect. Pharmacokinetics have not been specifically studied in different ethnic groups.

Adolescent and paediatric population

Tenofovir exposure achieved in adolescent patients receiving oral daily doses of tenofovir disoproxil 245 mg was similar to exposures achieved in adults receiving once-daily doses of tenofovir disoproxil 245 mg.

Pharmacokinetic studies have not been performed with tenofovir disoproxil 245 mg tablets in children under 12 years or with renal impairment.

Renal impairment

Compared with patients with normal renal function, the mean tenofovir exposure increased from 2,185 ng·h/ml in subjects not infected by HIV or hepatitis B virus with creatinine clearance over 80 ml/minute to 3064 ng·hour/ml, 6009 ng·hour/ml and 15,985 ng·hour/ml in patients with mild, moderate and severe renal impairment respectively.

The dosing recommendations in patients with renal impairment, with increased dosing interval, are expected to result in higher peak plasma concentrations and lower Cmin 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) (creatinine clearance less than 10 ml/minute) requiring haemodialysis, between-dialysis tenofovir concentrations substantially increased over 48 hours achieving a mean Cmax of 1032 ng/ml and a mean AUC0-48hour of 42,857 ng·hour/ml. It is recommended that the dosing interval for tenofovir disoproxil 245 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 in non-haemodialysis patients with creatinine clearance < 10 ml/min and in patients with ESRD managed by peritoneal or other forms of dialysis have not been studied.

Hepatic impairment

A single 245-mg dose of tenofovir disoproxil was administered to non-HIV, non-HBV infected patients with varying degrees of hepatic impairment defined according to Child-Pugh-Turcotte 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 tenofovir Cmax and AUC0-∞ values were 223 ng/ml and 2050 ng·hour/ml, respectively, in normal subjects compared with 289 ng/ml and 2310 ng·hour/ml in subjects with moderate hepatic impairment, and 305 ng/ml and 2740 ng·hour/ml in subjects with severe hepatic impairment.

Intracellular pharmacokinetics

Tenofovir diphosphate has an intracellular half-life of 10 hours in activated and 50 hours in resting peripheral blood mononuclear cells (PBMCs).

The absorption characteristics of Tenolaurus 300mg Tablets have been determined in healthy volunteers as follows:

Characteristic	**Arithmetic mean ± Standard deviation (Geometric mean)**
Maximum concentration (Cmax)	433 ± 112 ng/ml (420)
Area under the curve (AUC0-∞), a measure of the extent of absorption	3278 ± 651 ng.h/ml (3205)
to attain maximum concentration (Tmax)#	0.67 (0.33-1.25) hours

5.3 Preclinical safety data

Non-clinical safety pharmacology studies reveal no special hazard for humans. Findings in repeated dose toxicity studies in rats, dogs and monkeys at exposure levels greater than or equal to clinical exposure levels and with possible relevance to clinical use include renal and bone toxicity and a decrease in serum phosphate concentration. Bone toxicity was diagnosed as osteomalacia (monkeys) and reduced bone mineral density (BMD) (rats and dogs). The bone toxicity in young adult rats and dogs occurred at exposures ≥ 5-fold the exposure in paediatric or adult patients; bone toxicity occurred in juvenile infected monkeys at very high exposures following subcutaneous dosing (≥ 40-fold the exposure in patients). Findings in the rat and monkey studies indicated that there was a substance-related decrease in intestinal absorption of phosphate with potential secondary reduction in BMD.

Genotoxicity studies revealed positive results in the in vitro mouse lymphoma assay, equivocal results in one of the strains used in the Ames test, and weakly positive results in an UDS test in primary rat hepatocytes.

However, it was negative in an in vivo mouse bone marrow micronucleus assay.

Oral carcinogenicity studies in rats and mice revealed only a low incidence of duodenal tumours at an extremely high dose in mice. These tumours are unlikely to be of relevance to humans.

Reproductive studies in rats and rabbits showed no effects on mating, fertility, pregnancy or fetal parameters. However, tenofovir disoproxil reduced the viability index and weight of pups in peri-postnatal toxicity studies at maternally toxic doses.

The active substance tenofovir disoproxil and its main transformation products are persistent in the environment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate, microcrystalline cellulose, pregelatinized starch, croscarmellose sodium and magnesium stearate

Film-coating

Hypromellose, lactose monohydrate, titanium dioxide, triacetin, FD&C Blue #2/Indigo Carmine AL and FD&C Blue #2/Indigo Carmine Aluminum Lake

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

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

6.5 Nature and contents of container

30's Count: White opaque 60 cc HDPE bottles filled with 1gm silica gel canister, polyester coil closed with 33 mm child resistant closures.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORIZATION HOLDER

Laurus Labs Limited

2nd Floor, Serene Chambers, Road No.-7
Banjara Hills, Hyderabad – 500034.
India

8. MARKETING AUTHORISATION NUMBER(S)

Registration No: 04548/07032/NMR/2018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Oct 19, 2021

10. DATE OF REVISION OF THE TEXT

September 2023