WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]

The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/prequal/sites/default/files/document_files/75%20SRA%20clarification_Feb2017_newtempl.pdf

†Formerly Strides Shasun Limited.

1. NAME OF THE MEDICINAL PRODUCT

[HA535 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains tenofovir disoproxil fumarate 300 mg (equivalent to tenofovir disoproxil 245 mg).

Excipients with potential clinical effect

Each tablet contains about 153 mg lactose (as monohydrate).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

[HA535 trade name] is white, round, film-coated tablets. They are biconvex (rounded on top and bottom) with a bevelled edge. The tablets have "TDF" debossed (stamped into) on one side and are plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prevention of HIV infection

Treatment of HIV

[HA535 trade name] is indicated in combination with other antiretroviral medicinal products for the treatment of HIV infection in adults and adolescents weighing at least 30 kg.

HIV pre-exposure prophylaxis (PrEP)

[HA535 trade name] is indicated for pre-exposure prophylaxis (PrEP) for adults and adolescents weighing at least 30 kg who are at substantial risk of HIV infection, as part of combination prevention approaches.

HIV post-exposure prophylaxis (PEP)

[HA535 trade name] is indicated, in combination with other antiretroviral medicines, for post-exposure prophylaxis (PEP) in adults and adolescents weighing at least 30 kg who have been exposed to HIV.

HIV treatment and prophylaxis regimens should follow the most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

Hepatitis B infection

Treatment of chronic hepatitis B

[HA535 trade name] is indicated for the treatment of chronic hepatitis B in adults and adolescents from 12 years of age with any of the following features:

- Evidence of significant fibrosis or evidence of cirrhosis based on clinical criteria;
- Hepatitis B virus (HBV) DNA > 2000 IU/mL and alanine aminotransferase (ALT) level above the upper limit of normal (ULN) *or*, if HBV DNA assay is not available, persistently raised ALT levels over 6 to 12 months;

† Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

- Presence of coinfections (such as with HIV, hepatitis C or D); a family history of liver cancer or cirrhosis; immune suppression; comorbidities (such as diabetes, liver steatosis); or extrahepatic manifestations of HBV infection (such as glomerulonephritis or vasculitis).

Prevention of mother-to-child transmission of hepatitis B virus

[HA535 trade name] is indicated for preventing mother-to-child transmission of hepatitis B in HBV-positive pregnant women at high risk of transmitting the virus to their baby (those with HBV DNA ≥ 200 000 IU/mL or positive HBeAg). It may also be considered in all HBV-positive pregnant women when tests for HBV DNA or HBeAg are not available. Use to prevent mother-to-child transmission should be in accordance with official treatment guidelines for hepatitis B (e.g. those issued by the WHO).

HBV treatment regimens should follow the most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

4.2 Posology and method of administration

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

Posology

HIV infection

The recommended dose of [HA535 trade name] for the treatment of HIV in patients weighing 30 kg or more is 1 tablet (300 mg) once daily.

Daily pre-exposure prophylaxis (PrEP) of HIV

The recommended dose of [HA535 trade name] for daily PrEP is 1 tablet once a day. Daily PrEP should start 7 days before a person's potential exposure. When intending to stop daily PrEP, the person should have PrEP for 7 days after the last potential exposure.

Event-driven PrEP of HIV for adult males not taking exogenous estradiol-based hormones

Adult males who are not taking exogenous estradiol-based hormones can also have event-driven PrEP. For event-driven PrEP, the person should take 2 tablets 2 to 24 hours before potential exposure and then continue with 1 tablet once a day until 2 days after the last potential exposure.

Post-exposure prophylaxis (PEP) of HIV

The recommended dose of [HA535 trade name] for PEP is 1 tablet once daily for 28 days. PEP should start as early as possible after exposure and ideally within 72 hours of exposure.

Chronic hepatitis B

The recommended dose of [HA535 trade name] for the treatment of chronic hepatitis B in adults and adolescents from 12 years of age is 1 tablet (300 mg) once daily.

Duration of hepatitis B treatment

Antiviral hepatitis B treatment is lifelong. Discontinuation of treatment may be considered exceptionally for people without clinical evidence of cirrhosis:

- who can be followed carefully after discontinuation and long term for reactivation, and
- if there is evidence of HBeAg loss and seroconversion to anti-HBe (for people initially HBeAg-positive) and after completion of at least 1 additional year of treatment, and
- in association with persistently normal ALT levels and persistently undetectable HBV DNA levels (if HBV DNA testing is available).

If HBV DNA testing is not available: discontinuing therapy may be considered for people who have evidence of persistent HBsAg loss and after completion of at least 1 additional year of treatment, regardless of previous HBeAg status.

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

If treatment with [HA535 trade name] 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).

In adult patients with decompensated liver disease or cirrhosis, treatment cessation is not recommended.

Retreatment of chronic hepatitis B

Relapse is common after stopping therapy with [HA535 trade name]. Retreatment is recommended if there are consistent signs of reactivation: HBsAg or HBeAg becomes positive, ALT levels increase, or HBV DNA becomes detectable again.

Paediatric population

[HA535 trade name] should not be used in children and adolescents weighing less than 30 kg.

Elderly

There is no need for dose adjustment of [HA535 trade name] in the elderly.

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

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)

[HA535 trade name] should not be used for PrEP in HIV-1 uninfected individuals with estimated creatinine clearance below 60 ml/minute.

For HIV-therapy, administration of [HA535 trade name] every 48 hours is recommended in patients with moderate renal impairment (creatinine clearance 30-49 ml/minute), but the clinical response to treatment should be closely monitored in such patients (see sections 4.4 and 5.2).

For treatment of hepatitis B, [HA535 trade name] should not be started in patients with creatinine clearance below 50 ml/minute. For patients already on treatment with [HA535 trade name] the dosing interval should be extended to 48 hours and renal function should be closely monitored.

Severe renal impairment (creatinine clearance < 30 ml/minute) and haemodialysis patients:

For patients with no alternative treatment available, [HA535 trade name] may be used with prolonged dose intervals as follows:

- Severe renal impairment: [HA535 trade name] administered every 72-96 hours (dosing twice a week).
- Haemodialysis patients: [HA535 trade name] administered every 7 days or after completion of 12 hours cumulative haemodialysis.

Hepatic impairment

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

Missed dose and vomiting after a dose

If a patient misses a dose of [HA535 trade name] 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 [HA535 trade name] 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 [HA535 trade name], another tablet should be taken. There is no need to take an extra dose if the patient vomits more than 1 hour after taking [HA535 trade name].

Method of administration

[HA535 trade name] should be swallowed whole with food.

For patients who cannot swallow tablets, 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.

Use for pre-exposure prophylaxis in individuals with unknown or positive HIV status.

4.4 Special warnings and precautions for use

General

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

HIV pre-exposure prophylaxis (PrEP)

The effectiveness of tenofovir disoproxil PrEP in reducing the risk of acquiring HIV correlates strongly with adherence as demonstrated by drug levels in clinical trials. (For information on risk reduction seen with pre-exposure prophylaxis in trials, see section 5.1). Use of [HA535 trade name] for pre-exposure prophylaxis should be combined with other prevention measures, such as safer sex practices, as part of a comprehensive prevention strategy to further lower the risk of acquisition of HIV.

Uninfected individuals should be advised of the importance of strict adherence to the recommended dosing schedule and counselled about safer sex practices that include consistent and correct use of condoms, knowledge of their HIV 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).

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

Only an individual who has been confirmed HIV-negative should use [HA535 trade name] to prevent acquiring HIV infection. Use of tenofovir disoproxil alone in an individual with undetected HIV infection can lead to the virus developing resistance to the drug. Individuals with HIV infection must be treated with a combination of antiretrovirals.

Many HIV tests, such as rapid tests, detect anti-HIV antibodies and may not identify HIV during the acute stage of infection. Prior to beginning [HA535 trade name] for PrEP, 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 (e.g. from unprotected, or condom breakage during sex with an HIV 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, PrEP should be delayed for at least one month. The person’s HIV status should be confirmed before starting [HA535 trade name] for pre-exposure prophylaxis using a reliable test.

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

Pharmacological studies suggest that the time elapsing before oral PrEP with emtricitabine and tenofovir disoproxil is effective is 4 doses for anal sex and 7 doses for vaginal sex. People who report exposure to HIV before protection from PrEP has been achieved should be considered for post-exposure prophylaxis.

Post-exposure prophylaxis (PEP) regimen

Individuals should be counselled to adhere to the recommended 28-day dosing schedule for PEP. Adherence to a full 28-day course of antiretroviral drugs for post-exposure prophylaxis is critical to the effectiveness of the intervention.

Co-administration of other medicinal products

[HA535 trade name] should not be given with any other medicinal products containing tenofovir (either tenofovir disoproxil or tenofovir alafenamide) or its analogue adefovir dipivoxil, and use with other nephrotoxic medicines should also be avoided (see under Renal effects, below).

For more information on other medicines whose use with [HA535 trade name] should be avoided or requires caution, see section 4.5.

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.

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 when co-administered with 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 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.

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).

Prior to initiating [HA535 trade name] for the treatment of HIV/hepatitis B infection or for use in HIV pre-exposure prophylaxis, baseline renal function may be assessed.

In individuals without risk factors for renal disease, it is recommended that renal function (creatinine clearance and serum phosphate) is monitored annually.

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

Pre-exposure prophylaxis

[HA535 trade name] 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 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 [HA535 trade name], 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 [HA535 trade name] 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.

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).

Co-administration and risk of renal toxicity

Use of tenofovir disoproxil should be avoided with concurrent use of a *nephrotoxic medicine* (e.g. 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 tenofovir disoproxil 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 tenofovir disoproxil with a boosted protease inhibitor should be carefully evaluated.

Tenofovir disoproxil has not been clinically evaluated in patients receiving medicinal products which are secreted by the same renal pathway, including the transport proteins human organic anion transporter (hOAT) 1 and 3 or MRP 4 (e.g. cidofovir, a known nephrotoxic medicinal product). These renal transport proteins may be responsible for tubular secretion and in part, renal elimination of tenofovir and cidofovir. Consequently, the pharmacokinetics of these medicinal products, which are secreted by the same renal pathway including transport proteins hOAT 1 and 3 or MRP 4, might be modified if they are co-administered. Unless clearly necessary, concomitant use of these medicinal products which are secreted by the same renal pathway is not recommended, but if such use is unavoidable, renal function should be monitored weekly (see section 4.5).

Bone effects in adults

Bone abnormalities such as osteomalacia which can manifest as persistent or worsening bone pain and, which can infrequently contribute to fractures may be associated with tenofovir disoproxil induced proximal renal tubulopathy (see section 4.8).

Reductions of bone mineral density (BMD) have been observed with tenofovir disoproxil in randomized controlled clinical trials of duration up to 144 weeks in HIV or HBV-infected patients (see section 4.8 and 5.1). These BMD decreases generally improved after treatment discontinuation. In other studies (prospective and cross-sectional), the most pronounced decreases in BMD were seen in patients treated with tenofovir disoproxil as part of a regimen containing a boosted protease inhibitor.

Overall, in view of the bone abnormalities associated with tenofovir disoproxil and the limitations of long-term data on the impact of tenofovir disoproxil on bone health and fracture risk, alternative treatment regimens should be considered for patients with osteoporosis or with a history of bone fractures.

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 benefit against the 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. 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 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').

Weight and metabolism

An increase in weight and in the 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

[HA535 trade name] contains lactose. Lactose is a source of glucose and galactose. The small amount of lactose in each dose is unlikely to cause symptoms of lactose intolerance in other patients'. If, however, you have one of the rare genetic disorders galactosaemia, glucose-galactose intolerance or congenital lactase deficiency you must talk to your health care provider before taking this medicine.

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.

Concomitant use not recommended

[HA535 trade name] should not be administered with any other medicines containing:

- tenofovir disoproxil
- tenofovir alafenamide
- adefovir dipivoxil
- didanosine

Co-administration of tenofovir disoproxil and didanosine is not recommended because the risk of didanosine-related adverse events may increase. 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.

Renally eliminated medicinal products:

Since tenofovir is primarily eliminated by the kidneys, co-administration of tenofovir disoproxil with medicines 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 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.

Triple therapy with nucleosides/nucleotides

For a suggestion of reduced efficacy when tenofovir disoproxil was combined with lamivudine and abacavir or lamivudine and didanosine, see section 4.4.

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 and other medicinal products

Medicinal products 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/Ritonavir (300 mg/100 mg once daily)	Atazanavir: AUC: ↓ 25% C_{max}: ↓ 28%	No dose adjustment is recommended. The increased exposure of tenofovir could

Medicinal products 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**
	C_{min}: ↓ 26% Tenofovir: AUC: ↑ 37% C_{max}: ↑ 34% C_{min}: ↑ 29%	potentiate tenofovir-associated 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 pharmacokinetic 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 pharmacokinetic 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.
Adefovir dipivoxil	Adefovir dipivoxil: AUC: ↓ 11% (↓ 14 to ↓ 7) C_{max}: ↓ 7% (↓ 13 to ↓ 0) Tenofovir: AUC: ↓ 2% (↓ 5 to ↑ 0) C_{max}: ↓ 1% (↓ 7 to ↑ 6)	Tenofovir disoproxil should not be administered concurrently with adefovir dipivoxil.
Hepatitis C virus antiviral agents		
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) +	Ledipasvir: AUC: ↑ 96%	Increased plasma concentrations of tenofovir resulting from co-

Medicinal products 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**
Atazanavir/Ritonavir (300 mg q.d./100 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)[1]	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}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↑ 47% C_{min}: ↑ 47%	administration of tenofovir disoproxil, ledipasvir/sofosbuvir and atazanavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil 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).
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Darunavir/Ritonavir (800 mg q.d./100 mg q.d.) + Emtricitabine/Tenofovir disoproxil (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:	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, ledipasvir/sofosbuvir and darunavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil 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).

Medicinal products 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**
	AUC: ↔ C_{max}: ↔ C_{min}: ↑ 48% Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 50% C_{max}: ↑ 64% C_{min}: ↑ 59%	
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Efavirenz/Emtricitabine/Tenofovir disoproxil (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, 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 (200 mg/25 mg/245 mg q.d.)	Ledipasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2]:	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).

Medicinal products 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**
	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%	
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: ↔ C_{max}: ↔ C_{min}: ↔ Dolutegravir AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 65% C_{max}: ↑ 61% C_{min}: ↑ 115%	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.) + Atazanavir/Ritonavir (300 mg q.d./100 mg q.d.) + Emtricitabine/Tenofovir disoproxil	Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2:]	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, sofosbuvir/velpatasvir and atazanavir/ritonavir may

Medicinal products 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**
(200 mg/245 mg q.d.)	AUC: ↔ C_{max}: ↔ C_{min}: ↑ 42% Velpatasvir: AUC: ↑ 142% C_{max}: ↑ 55% C_{min}: ↑ 301% Atazanavir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 39% Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 29% Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↑ 55% C_{min}: ↑ 39%	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).
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% C_{max}: ↓ 38% GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Velpatasvir: AUC: ↔ C_{max}: ↓ 24% C_{min}: ↔ Darunavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔	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).

Medicinal products 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**
	Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 39% C_{max}: ↑ 55% C_{min}: ↑ 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% C_{max}: ↓ 41% GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Velpatasvir: AUC: ↔ C_{max}: ↓ 30% C_{min}: ↑ 63% Lopinavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↑ 42% C_{min}: ↔	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).
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: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔	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

Medicinal products 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**
	Velpatasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Raltegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↓ 21% Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 40% C_{max}: ↑ 46% C_{min}: ↑ 70%	4.4).
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Efavirenz/Emtricitabine/Tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ C_{max}: ↑ 38% GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Velpatasvir: AUC: ↓ 53% C_{max}: ↓ 47% C_{min}: ↓ 57% Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 81% C_{max}: ↑ 77% C_{min}: ↑ 121%	Concomitant administration of sofosbuvir/velpatasvir and efavirenz is expected to decrease plasma concentrations of velpatasvir. Co-administration of sofosbuvir/velpatasvir with efavirenz-containing regimens is not recommended.
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Emtricitabine/Rilpivirine/Tenofovir	Sofosbuvir: AUC: ↔ C_{max}: ↔	No dose adjustment is recommended. The increased exposure of tenofovir could

Medicinal products 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**
disoproxil (200 mg/25 mg/245 mg q.d.)	GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Velpatasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Rilpivirine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 40% C_{max}: ↑ 44% C_{min}: ↑ 84%	potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4).
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: ↔ C_{max}: ↓ 30% C_{min}: N/A GS-331007[2]: AUC: ↔ C_{max}:↔ C_{min}: N/A Velpatasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Voxilaprevir: AUC: ↑ 143% C_{max}:↑ 72% C_{min}: ↑ 300% Darunavir: AUC: ↔ C_{max}: ↔ C_{min}: ↓ 34% Ritonavir:	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).

Medicinal products 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**
	AUC: ↑ 45% C_{max}: ↑ 60% C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 39% C_{max}: ↑ 48% C_{min}: ↑ 47%	
Sofosbuvir (400 mg q.d.) + Efavirenz/Emtricitabine/Tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ C_{max}: ↓ 19% GS-331007[2]: AUC: ↔ C_{max}: ↓ 23% Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↑ 25% C_{min}: ↔	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 with other medicines

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

Food effect

Food enhances the bioavailability of tenofovir (see section 5.2). Therefore, tenofovir disoproxil should be taken with food.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

Tenofovir disoproxil can be used during pregnancy.

A large amount of data on pregnant women (more than 1,000 pregnancy outcomes) indicate no malformations or fetal/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).

Breast-feeding

Although some tenofovir disoproxil is present in human milk, the medicine may be used during breast-feeding.

Current recommendations on breast-feeding in women with HIV and HBV infection (e.g. those from the WHO) should be consulted. 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

Summary of the safety profile

HIV treatment: 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 increases adverse reactions (see section 4.5). Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported.

Pre-exposure prophylaxis (PrEP): 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. The most frequently reported adverse effects were abdominal pain (up to 12%) and nausea (10%).

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).

Tabulated summary of adverse reactions

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

Common	Bone mineral density decreased [3]
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, proximal renal tubulopathy (including Fanconi syndrome)
Rare	acute renal failure, renal failure, acute tubular necrosis, 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.

[3] The frequency of this adverse reaction was estimated based on safety data derived from different clinical studies with TDF in HBV infected patients.

Pre-exposure prophylaxis

In individual studies of tenofovir disoproxil for PrEP, 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 phosphorus grade 1 (16% vs. 14%), AST elevations grade 1/2 (2% vs 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 and hepatitis B

Renal impairment

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.

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.

Lactic acidosis

Cases of lactic acidosis have been reported with tenofovir disoproxil alone or in combination with other antiretrovirals. Patients with predisposing factors such as patients with decompensated liver disease, or patients receiving concomitant medications known to induce lactic acidosis are at increased risk of experiencing severe lactic acidosis during tenofovir disoproxil treatment, including fatal outcomes.

HIV

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 $\geq$ 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 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, 8 out of 89 paediatric patients treated with tenofovir disoproxil (median tenofovir disoproxil treatment 331 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 m^2. Among them, 3 patients had a clinically meaningful decline in estimated GFR which improved after discontinuation of tenofovir disoproxil.

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).

Other special populations

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 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.

Reporting of suspected adverse reactions

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

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 can be removed by haemodialysis; the median haemodialysis clearance of tenofovir is 134 ml/minute. 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 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 HIV_{BaL} 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

<u>HIV-1 therapy</u>

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

Daily HIV 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%, $p = 0.01$).

HIV event-driven pre-exposure prophylaxis (ED-PrEP)

Data from trials, open label extension studies and demonstration studies have shown that oral PrEP using the ED-PrEP dosing regimen is as effective in preventing HIV infection as daily PrEP in cisgender men who have sex with men. As a result, the WHO concluded that an ED-PrEP regimen is safe and highly effective in reducing risk of HIV acquisition through receptive and/or insertive sex between cisgender men and can be offered as an alternative to daily dosing for men who have sex with men. Importantly, ED-PrEP is effective for all positioning (insertive and/or receptive). It is reasonable to extrapolate that the risk of HIV associated with cisgender men having sex with cisgender men should not be lower than for cisgender men having sex with individuals from other populations. Similarly, for trans and gender diverse people assigned male at birth who are not taking exogenous estradiol-based hormones, the risk of HIV acquisition from anal sex should be similar to the risk in cisgender men.

There is insufficient evidence to support the efficacy of ED-PrEP dosing regimens for other groups, including people with injecting exposure, people assigned female at birth, and people assigned male at birth who are taking estradiol-based hormones. Small studies have suggested that the use of gender affirming hormones may reduce the concentrations of tenofovir disoproxil fumarate and emtricitabine among transgender women by 12–27%, although this has been questioned. While the lower PrEP concentration is unlikely to affect the efficacy of daily oral PrEP, effects on ED-PrEP dosing efficacy are unclear and further studies are needed.

HIV post-exposure prophylaxis

A systematic review completed in 2018 assessed the tolerability of HIV PEP and completion of different antiretroviral drug regimens. The systematic review identified 16 studies reporting the outcomes of HIV PEP regimens using tenofovir disoproxil fumarate/lamivudine (or emtricitabine) backbones. All studies involved adults, and no additional evidence was retrieved for PEP regimens for children or adolescents.

Overall, the highest completion rates for HIV PEP were reported for tenofovir disoproxil fumarate/lamivudine (or emtricitabine) in combination with darunavir/ritonavir (93%, 95% CI 89–97%) or dolutegravir (90%, 95% CI 84–96%). These regimens were also associated with the lowest rates of discontinuation or substitutions because of adverse events (1%, 95% CI 0–2% for darunavir/ritonavir; 1%, 95% CI 1–4% for dolutegravir).

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 and/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 are displayed in the table below.

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.

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.

Parameter	**HBeAg negative**		**HBeAg positive**	
	Tenofovir disoproxil 245 mg n = 250	Adefovir dipivoxil 10 mg n = 125	Tenofovir disoproxil 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) Week 48	93*	63	76*	13
HBV DNA (%) < 169 copies/ml (< 29 IU/ml) Week 48	91*	56	69*	9

* p-value *versus* adefovir dipivoxil < 0.05

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

Seventy-seven percent and 61% of patients continued in the studies through to 384 weeks, respectively. At weeks 96, 144, 192, 240, 288 and 384, viral suppression, biochemical and serological responses were maintained with continued tenofovir disoproxil treatment. Paired baseline and week 240 liver biopsy data were available for 331/489 patients who remained in studies. Ninety-five percent (225/237) of patients without cirrhosis at baseline and 99% (93/94) of patients with cirrhosis at baseline had either no change or an improvement in fibrosis. Of the 94 patients with cirrhosis at baseline (Ishak fibrosis score: 5 - 6), 72% (68) experienced regression of cirrhosis by week 240 with a reduction in Ishak fibrosis score of at least 2 points.

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 bi-therapy 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 patients with decompensated liver disease.

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. Overall, the data derived from this study are too limited to draw any definitive conclusions on the comparison of emtricitabine plus tenofovir disoproxil versus tenofovir disoproxil.

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, 83% (117/141) randomised to tenofovir disoproxil had HBV DNA < 400 copies/ml, and 65% (51/79) had ALT normalisation. After 240 weeks of treatment with emtricitabine plus tenofovir disoproxil, 83% (115/139) had HBV DNA < 400 copies/ml, and 59 of 83 subjects (71%) had ALT normalisation.

Among the HBeAg positive subjects randomised to tenofovir disoproxil, 25% (16/65) experienced HBeAg loss, and 12% (8/65) experienced anti-HBe seroconversion through week 240. In the HBeAg positive subjects randomised to emtricitabine plus tenofovir disoproxil, 19% (13/68) experienced HBeAg loss, and 10% (7/68) experienced anti-HBe seroconversion through week 240.

Clinical resistance

In 821 adults 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 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 normalisation 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 (BL)		**Week 72**		**Week 192**	
	Tenofovir disoproxil-tenofovir disoproxil	**PLB-tenofovir disoproxil**	**Tenofovir disoproxil-tenofovir disoproxil**	**PLB-tenofovir disoproxil**	**Tenofovir disoproxil-tenofovir 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 BL 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 BL 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 subject)
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

The absorption characteristics of [HA535 trade name] have been determined after administration of single tablets in healthy volunteers in the fasted state as follows:

Pharmacokinetic variable	**Mean value* (± standard deviation)**
Maximum concentration (C_{max})	287 (±78) ng/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	2253 (±647) ng·h/mL
Time to attain maximum concentration (t_{max})	1.0 (± 0.42) h

***** Arithmetic mean

Pharmacokinetics of Tenofovir disoproxil

<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 colspan="2">Absorption</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>$AUC_{(0-\infty)}$</td><td>C_{max}</td><td>T_{max}</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>1h↑</td></tr>
</table>
</td></tr>
<tr><td colspan="2">Distribution</td></tr>
<tr><td>Volume of distribution (mean)</td><td>800 ml/kg</td></tr>
<tr><td>Plasma proteinbindingin vitro</td><td><0.7 % (serum protein binding <7.2%)</td></tr>
<tr><td>Tissue distribution</td><td>Well distributed, with highest concentrations in kidney and liver.</td></tr>
<tr><td colspan="2">Metabolism</td></tr>
<tr><td></td><td>In vitro studies have determined that neither tenofovir disoproxil nor tenofovir is a substrate for the CYP450 enzymes.</td></tr>
<tr><td>Active metabolite(s)</td><td>Tenofovir</td></tr>
<tr><td colspan="2">Elimination</td></tr>
<tr><td>Elimination half life</td><td>Tenofovir: 12 to 18 h
Tenofovir diphosphate: 10 h in intracellular activated resting peripheral blood mononuclear cells and 50 hours in resting peripheral blood mononuclear cells.</td></tr>
<tr><td>Mean systemic clearance (Cl/F)</td><td>0.23 L/h/kg</td></tr>
<tr><td>% of dose excreted in urine</td><td>70-80% as unchanged drug</td></tr>
</table>

% 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

* NA: Not available

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·hour/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 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) (creatinine clearance less than 10 ml/minute) requiring haemodialysis, between-dialysis tenofovir concentrations substantially increased over 48 hours achieving a mean C_{max} of 1032 ng/ml and a mean $AUC_{0\text{-}48hour}$ 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 C_{max} and $AUC_{0\text{-}\infty}$ 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.

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

Core tablet: Croscarmellose sodium,
lactose monohydrate,
microcrystalline cellulose,
pregelatinised starch,
magnesium stearate.

Film coat: Hypromellose,
polyethylene glycol,
titanium dioxide.

This medicine is essentially 'sodium-free'. It contains less than 1 mmol sodium (23 mg) per *tablet*.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30ºC. Protect from moisture.

6.5 Nature and contents of container

Al/Al cold form blisters

[HA535 trade name] is provided in aluminium-aluminium cold form blister cards, each containing 10 tablets. Available in boxes of 3×10 tablets.

HDPE

Round, white opaque HDPE bottle containing 30 tablets. It also contains silica gel sachet as desiccant. The bottle is sealed with a white opaque screw cap with induction sealed liner.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7. SUPPLIER

Strides Pharma Science Limited
Strides House, Opp. IIMB,
Bilekahalli,
Bannerghatta Road,
Bangalore – 560 076
India.
Tel: +91-80-6784 0000
E-mail: corpcomm@strides.com

8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

HA535

9. DATE OF PREQUALIFICATION

21 October 2013

10. DATE OF REVISION OF THE TEXT

March 2025

References

European SmPC, Viread. Available at https://www.ema.europa.eu/documents/product-information/viread-epar-product-information_en.pdf

European SmPC, Truvada, available at: https://www.ema.europa.eu/en/documents/product-information/truvada-epar-product-information_en.pdf

UK SmPC, Tenofovir disoproxil 245 mg film-coated tablets (Cipla), available at: https://www.medicines.org.uk/emc/product/9932/smpc

WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, 2021. Available at: https://www.who.int/publications/i/item/9789240031593

WHO. Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection. Geneva, 2024. Available at: https://iris.who.int/bitstream/handle/10665/376353/9789240090903-eng.pdf?sequence=1

WHO. Consolidated guidelines on HIV, viral hepatitis and STI prevention, diagnosis, treatment and care for key populations 2022 update. Available at: https://www.who.int/publications/i/item/9789240052390

WHO. Differentiated and simplified pre-exposure prophylaxis for HIV prevention. Update to WHO implementation guidance, 2022. Available at: https://www.who.int/publications/i/item/9789240053694

WHO. Guidelines for HIV post-exposure prophylaxis. Geneva, 2024. Available at: https://iris.who.int/bitstream/handle/10665/378221/9789240095137-eng.pdf?sequence=1

WHO. Guidelines on post-exposure prophylaxis for HIV and the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children: recommendations for a public health approach. Geneva, 2014. Available at: https://www.who.int/publications/i/item/9789241506830

What's the 2+1+1? Event-driven oral pre-exposure prophylaxis to prevent HIV for men who have sex with men: Update to WHO's recommendation on oral PrEP; 2019. Available at: https://www.who.int/publications/i/item/what-s-the-2-1-1-event-driven-oral-pre-exposure-prophylaxis-to-prevent-hiv-for-men-who-have-sex-with-men

Baeten JM et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *NEJM* 2012, 367: 399-410

Choopanya K et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomized, double-blind, placebo-controlled phase 3 trial. *Lancet* 2013; 381: 2083-90

Grohskopf LA et al. Randomized trial of clinical safety of daily oral tenofovir disoproxil fumarate among HIV-uninfected men who have sex with men in the United States. *J Acquir Immune Defic Syndr* 2013; 64: 79-86

Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/prequal/medicines/prequalified/finished-pharmaceutical-products