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 (term to be revised).
The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

1. NAME OF THE MEDICINAL PRODUCT

[HA414 trade name]*

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:
Lamivudine 300 mg
Tenofovir disoproxil fumarate 300 mg (equivalent to tenofovir disoproxil 24 mg or tenofovir 136 mg)

Each tablet contains 168 mg lactose monohydrate.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

White to off white coloured, oval shaped, biconvex, film-coated tablets debossed "M112" on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[HA414 trade name] is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in patients weighing at least 30 kg or more.

The choice of [HA414 trade name] to treat antiretroviral-experienced patients with HIV-1 infection should be based on individual viral resistance testing or the treatment history of the patient.

[HA414 trade name] 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.

4.2 Posology and method of administration

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

Posology

Adult and adolescents

The recommended dose of [HA414 trade name] is one tablet, taken once daily.

For PrEP, alternative dose recommendations may apply to specific subgroups of HIV-1 uninfected individuals at risk for HIV-infection. For use of [HA414 trade name] for PrEP, consult the most recent official guidelines, e.g. those by WHO.

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

Special populations

Children and adolescents

HIV-therapy: [HA414 trade name] 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 substances are available.
PrEP: [HA414 trade name] should not be used in adolescents weighing less than 35 kg due to insufficient data on safety and efficacy (see section 5.2).

Elderly

[HA414 trade name] should be administered with caution to elderly patients (see section 4.4).

Renal impairment

[HA414 trade name] is not recommended for use in patients with creatinine clearance < 50 ml/minute (see sections 4.4. and 5.2), as appropriate dose adjustments are not possible. For these patients, separate formulations of lamivudine and tenofovir disoproxil should be used.

[HA414 trade name] should not be used for PrEP in HIV-1 uninfected individuals with estimated creatinine clearance below 60 ml/minute.

Hepatic impairment

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

Discontinuation of therapy

Where discontinuation of therapy of HIV-1 infection with one of the components of [HA414 trade name] is indicated or where dose modification is necessary, separate preparations of lamivudine and tenofovir disoproxil should be used. If [HA414 trade name] is discontinued in patients co-infected with HIV and hepatitis B virus (HBV), these patients should be closely monitored for evidence of exacerbation of hepatitis (see section 4.4).

Advice on missed dose

If a dose of [HA414 trade name] is missed within 12 hours of the time it is usually taken, the individual should take the medicine as soon as possible and resume the normal dosing schedule with the next due dose.

If the patient misses a dose of [HA414 trade name] by more than 12 hours and it is almost time for the next dose, the individual should not take the missed dose and simply resume the usual dosing schedule.

If the individual vomits within 1 hour of taking [HA414 trade name], another tablet should be taken. There is no need to take an extra dose if vomiting occurs more than 1 hour after taking [HA414 trade name].

Method of administration:

It is recommended that [HA414 trade name] be swallowed whole with water. [HA414 trade name] can be taken with food or between meals.

For young children or patients not able to swallow the tablets whole, the tablets may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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:

[HA414 trade name] 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).

Uninfected individuals should be counselled to strictly adhere to the recommended [HA414 trade name] 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.

Only an individual who has been confirmed HIV-negative should use [HA414 trade name] 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 [HA414 trade name] 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 [HA414 trade name]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.

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.

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

Transmission of HIV

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Mitochondrial dysfunction following exposure in utero

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

Weight and metabolic parameters

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

Immune Reactivation Syndrome

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

Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Opportunistic infections

HIV-1 infected patients receiving [HA414 trade name] or any other antiretroviral therapy may still develop opportunistic infections and other complications of HIV infection. Therefore patients should remain under close clinical observation by heath care providers experienced in the treatment of these associated HIV diseases.

Renal function

Lamivudine and tenofovir disoproxil are primarily excreted by the kidneys, through a combination of glomerular filtration and active tubular secretion. [HA414 trade name] is not recommended for patients with moderate or severe renal impairment (creatinine clearance < 50 ml/min). Patients with moderate or severe renal impairment require a dose adjustment of lamivudine and tenofovir disoproxil that cannot be achieved with the combination tablet (see sections 4.2 and 5.2).

Renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir disoproxil in clinical practice (see section 4.8).

It is recommended that creatinine clearance /estimated glomerular function is calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with [HA414 trade name]. If the creatinine test is routinely available, the estimated glomerular filtration rate at baseline should be used before initiating tenofovir disoproxil containing regimens.
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 patients (those who are older or have underlying renal disease, long-term diabetes or uncontrolled hypertension concomitant with boosted PIs or nephrotoxic drugs) to detect and limit further progression of renal impairment. Benefit and risks should be carefully weighed.

If available, also serum phosphate should be measured in these patients. If serum phosphate is < 1.5 mg/dl (0.48 mmol/l) or creatinine clearance is decreased to < 50 ml/min in any patient receiving this medicine renal function must be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations (see section 4.8, proximal tubulopathy).

Since [HA414 trade name] is a combination product and the dosing interval of the individual components cannot be altered, treatment with this medicine must be interrupted in patients with confirmed creatinine clearance < 50 ml/min or decreases in serum phosphate to < 1.0 mg/dl (0.32 mmol/l).
Interrupting treatment should also be considered in case of progressive decline of renal function when no other cause has been identified. Where discontinuation of therapy with one of the components is indicated or where dose modification is necessary, separate preparations of lamivudine and tenofovir disoproxil are available.

This medicine should be avoided with concurrent or recent use of a nephrotoxic medicinal product (e.g. high-dose or multiple non-steroidal anti-inflammatory drugs, aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir, interleukin-2). If concomitant use of [HA414 trade name] and nephrotoxic agents is unavoidable, renal function must be monitored weekly (see section 4.5).

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).

Pre-exposure Prophylaxis

[HA414 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.

Elderly

Elderly patients are more likely to have decreased renal function; therefore caution should be exercised when treating elderly patients with [HA414 trade name]

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 was not increased and there was no evidence of clinically relevant bone abnormalities.

In HIV-1 infected adolescents 12 years of age and older, the mean rate of bone gain was less in the tenofovir disoproxil -treated group compared to the placebo group. Skeletal growth (height) appeared to be unaffected. Markers of bone turnover in tenofovir disoproxil-treated adolescents suggest increased bone turnover, consistent with the effects observed in adults. Due to the possible effects of tenofovir on bone metabolism, [HA414 trade name] should only be used in adolescents under the age of 18 if the benefits are considered to exceed the risk (see also section 4.8).

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.

Osteonecrosis

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

Pancreatitis

Cases of pancreatitis have occurred rarely. However it is not clear whether these cases were due to the antiretroviral treatment or to the underlying HIV disease. Treatment with [HA414 trade name] should be stopped immediately if clinical signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur.

Liver disease

The safety and efficacy of [HA414 trade name] have not been established in patients with significant underlying liver disorders. Patients with pre-existing 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.

Safety and efficacy data of tenofovir disoproxil are very limited in liver transplant patients.

There are limited data on the safety and efficacy of tenofovir disoproxil in HBV infected patients with decompensated liver disease and who have a Child-Pugh-Turcotte (CPT) score > 9. These patients may be at higher risk of experiencing serious hepatic or renal adverse reactions. Therefore, hepatobiliary and renal parameters should be closely monitored in this patient population during treatment with lamivudine/tenofovir disoproxil.

Patients with HIV and hepatitis B (HBV) or C virus (HCV) co-infections

Health care providers should refer to current relevant treatment guidelines for the optimal management of HIV infection in patients co-infected with HBV or HCV.

Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk of severe and potentially fatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

Lamivudine and tenofovir disoproxil are also active against HBV. Therefore, discontinuation of [HA414 trade name] in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis. Patients co-infected with HIV and HBV who discontinue [HA414 trade name] should be closely monitored with both clinical and laboratory follow-up for at least six months after stopping treatment. If appropriate, resumption of hepatitis B therapy may be warranted. In patients with advanced liver disease or

cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

Exacerbations of hepatitis

Flares on treatment: Spontaneous exacerbations in 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 (see section 4.8). 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 also 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, resumption of hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.
Liver flares are especially serious, and sometimes fatal in patients with decompensated liver disease.

Antivirals against HCV

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.

Co-administration of other medicinal products

As a fixed combination, [HA414 trade name] should not be administered concomitantly with other medicinal products containing any of the same active components, lamivudine or tenofovir disoproxil.

Due to similarities with lamivudine, [HA414 trade name] should not be administered concomitantly with other cytidine analogues, such as emtricitabine. [HA414 trade name] should not be administered concomitantly with medicinal products containing adefovir dipivoxil or tenofovir alafenamide.

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

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

Triple therapy with nucleosides/nucleotides:

There have been reports of a high rate of virological failure and of early emergence of resistance in HIV patients when tenofovir disoproxil and lamivudine was combined with abacavir or didanosine as a once daily regimen.

Excipients
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

No drug interaction studies have been conducted using lamivudine/tenofovir disoproxil tablets. Drug interaction studies have been conducted with lamivudine or tenofovir disoproxil, the components of this fixed dose combination.

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

Interactions relevant to lamivudine

Sulfamethoxazole/trimethoprim increases plasma concentrations of lamivudine but a clinically significant effect is not expected; the patient should be monitored for lamivudine toxicity in case of marked renal impairment or if high doses of sulfamethoxazole/trimethoprim are used (e.g. for *Pneumocystis jirovecii* pneumonitis treatment).

Medicinal products, whose main route of elimination is active renal secretion via the organic cationic transport system, e.g. trimethoprim, may interact with lamivudine. Medicinal products (e.g. ranitidine, cimetidine), which are eliminated only in part by this mechanism, were shown not to interact with lamivudine.

Due to similarities, [HA414 trade name] should not be administered concomitantly with other cytidine analogues, such as emtricitabine. Moreover, [HA414 trade name] should not be taken with any other medicinal products containing lamivudine (see section 4.4).

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

Coadministration of sorbitol solution (3.2 g, 10.2 g, 13.4 g) with a single 300 mg dose of lamivudine oral solution resulted in dose-dependent decreases of 14%, 32%, and 36% in lamivudine exposure (AUC∞) and 28%, 52%, and 55% in the C_{max} of lamivudine in adults. When possible, chronic coadministration of lamivudine with medicinal products containing sorbitol or other osmotic acting polyalcohols or monosaccharide alcohols (e.g. xylitol, mannitol, lactitol, maltitol) should be avoided. More frequent monitoring of HIV-1 viral load, when chronic coadministration cannot be avoided, should be considered.

Interactions relevant to tenofovir

Concomitant use not recommended
[HA414 trade name] 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 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.

Other interactions:

Interactions between [HA414 trade name] 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, Cmax, Cmin**	**Recommendation on co-administration with tenofovir disoproxil 245 mg**
ANTI-INFECTIVES		
antiretrovirals		
Protease inhibitors		
Atazanavir (400 mg once daily)	Atazanavir: AUC: ↓ 25% Cmax: ↓ 21% Cmin: ↓ 40% Tenofovir: AUC: ↑ 24% Cmax: ↑ 14% Cmin: ↑ 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% Cmax: ↓ 28% Cmin: ↓ 26% Tenofovir: AUC: ↑ 37% Cmax: ↑ 34% Cmin: ↑ 29%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir-associated adverse events, including renal disorders. Renal function should be closely monitored (see section 4.4).
Lopinavir/Ritonavir (400 mg/100 mg twice daily.)	Lopinavir/ritonavir: No significant effect on lopinavir/ritonavir pharmacokinetic parameters.	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir-associated

Medicinal products by therapeutic areas (dose in mg)	**Effects on drug levels Mean % change in AUC, Cmax, Cmin**	**Recommendation on co-administration with tenofovir disoproxil 245 mg**
	Tenofovir: AUC: ↑ 32% Cmax: ↔ Cmin: ↑ 51%	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% Cmin: ↑ 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: ↔ Cmax: ↔	Tenofovir disoproxil should not be administered concurrently with adefovir dipivoxil (see section 4.4).
Entecavir	AUC: ↔ Cmax: ↔	No clinically significant pharmacokinetic interactions when tenofovir disoproxil 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 (200 mg/245 mg q.d.)[1]	Ledipasvir: AUC: ↑ 96% Cmax: ↑ 68% Cmin: ↑ 118% Sofosbuvir: AUC: ↔ Cmax: ↔ GS-331007[2]: AUC: ↔ Cmax: ↔	Increased plasma concentrations of tenofovir resulting from co-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.

Medicinal products by therapeutic areas (dose in mg)	**Effects on drug levels Mean % change in AUC, Cmax, Cmin**	**Recommendation on co-administration with tenofovir disoproxil 245 mg**
	Cmin: ↑ 42% Atazanavir: AUC: ↔ Cmax: ↔ Cmin: ↑ 63% Ritonavir: AUC: ↔ Cmax: ↔ Cmin: ↑ 45% Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↔ Cmax: ↑ 47% Cmin: ↑ 47%	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: ↔ Cmax: ↔ Cmin: ↔ Sofosbuvir: AUC: ↓ 27% Cmax: ↓ 37% GS-331007[2]: AUC: ↔ Cmax: ↔ Cmin: ↔ Darunavir: AUC: ↔ Cmax: ↔ Cmin: ↔ Ritonavir: AUC: ↔ Cmax: ↔ Cmin: ↑ 48% Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↑ 50%	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, Cmax, Cmin**	**Recommendation on co-administration with tenofovir disoproxil 245 mg**
	Cmax: ↑ 64% Cmin: ↑ 59%	
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Efavirenz/Emtricitabine/Tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)	Ledipasvir: AUC: ↓ 34% Cmax: ↓ 34% Cmin: ↓ 34% Sofosbuvir: AUC: ↔ Cmax: ↔ GS-331007[2]: AUC: ↔ Cmax: ↔ Cmin: ↔ Efavirenz: AUC: ↔ Cmax: ↔ Cmin: ↔ Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↑ 98% Cmax: ↑ 79% Cmin: ↑ 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: ↔ Cmax: ↔ Cmin: ↔ Sofosbuvir: AUC: ↔ Cmax: ↔ GS-331007[2]: AUC: ↔ Cmax: ↔ Cmin: ↔ Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Rilpivirine: AUC: ↔ Cmax: ↔	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, Cmax, Cmin**	**Recommendation on co-administration with tenofovir disoproxil 245 mg**
	Cmin: ↔ Tenofovir: AUC: ↑ 40% Cmax: ↔ Cmin: ↑ 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: ↔ Cmax: ↔ GS-331007[2] AUC: ↔ Cmax: ↔ Cmin: ↔ Ledipasvir: AUC: ↔ Cmax: ↔ Cmin: ↔ Dolutegravir AUC: ↔ Cmax: ↔ Cmin: ↔ Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↑ 65% Cmax: ↑ 61% Cmin: ↑ 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 (200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ Cmax: ↔ GS-331007[2:] AUC: ↔ Cmax: ↔ Cmin: ↑ 42% Velpatasvir: AUC: ↑ 142% Cmax: ↑ 55% Cmin: ↑ 301% Atazanavir: AUC: ↔ Cmax: ↔ Cmin: ↑ 39%	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).

Medicinal products by therapeutic areas (dose in mg)	**Effects on drug levels Mean % change in AUC, Cmax, Cmin**	**Recommendation on co-administration with tenofovir disoproxil 245 mg**
	Ritonavir: AUC: ↔ Cmax: ↔ Cmin: ↑ 29% Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↔ Cmax: ↑ 55% Cmin: ↑ 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: ↔ Cmin: ↔ Tenofovir: AUC: ↑ 39% Cmax: ↑ 55% Cmin: ↑ 52%	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).
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Lopinavir/Ritonavir (800 mg/200 mg q.d.) +	Sofosbuvir: AUC: ↓ 29% Cmax: ↓ 41%	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, sofosbuvir/velpatasvir

Medicinal products by therapeutic areas (dose in mg)	**Effects on drug levels Mean % change in AUC, Cmax, Cmin**	**Recommendation on co-administration with tenofovir disoproxil 245 mg**
Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)	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: ↔ Cmax: ↑ 42% Cmin: ↔	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: ↔ Cmax: ↔ GS-331007[2]: AUC: ↔ Cmax: ↔ Cmin: ↔ Velpatasvir: AUC: ↔ Cmax: ↔ Cmin: ↔ Raltegravir: AUC: ↔ Cmax: ↔ Cmin: ↓ 21% Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔	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, Cmax, Cmin**	**Recommendation on co-administration with tenofovir disoproxil 245 mg**
	Tenofovir: AUC: ↑ 40% Cmax: ↑ 46% Cmin: ↑ 70%	
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: ↔ Cmax: ↔ Cmin: ↔ Velpatasvir: AUC: ↓ 53% Cmax: ↓ 47% Cmin: ↓ 57% Efavirenz: AUC: ↔ Cmax: ↔ Cmin: ↔ Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↑ 81% Cmax: ↑ 77% Cmin: ↑ 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 disoproxil (200 mg/25 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ Cmax: ↔ GS-331007[2]: AUC: ↔ Cmax: ↔ Cmin: ↔ Velpatasvir: AUC: ↔ Cmax: ↔ Cmin: ↔ Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔	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, Cmax, Cmin**	**Recommendation on co-administration with tenofovir disoproxil 245 mg**
	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% Ritonavir: AUC: ↑ 45% Cmax: ↑ 60% Cmin: ↔ Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↑ 39% Cmax: ↑ 48% Cmin: ↑ 47%	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).
Sofosbuvir (400 mg q.d.) + Efavirenz/Emtricitabine/Tenofovir disoproxil	Sofosbuvir: AUC: ↔ Cmax: ↓ 19%	No dose adjustment is required.

Medicinal products by therapeutic areas (dose in mg)	Effects on drug levels Mean % change in AUC, Cmax, Cmin	Recommendation on co-administration with tenofovir disoproxil 245 mg
(600 mg/200 mg/245 mg q.d.)	GS-331007[2]: AUC: ↔ Cmax: ↓ 23% Efavirenz: AUC: ↔ Cmax: ↔ Cmin: ↔ Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↔ Cmax: ↑ 25% Cmin: ↔	

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 [HA414 trade name] was co-administered with indinavir, efavirenz, saquinavir (ritonavir boosted), methadone, ribavirin, rifampicin, tacrolimus, or the hormonal contraceptive norgestimate/ethinylestradiol.

Food effect

Food has no influence on the absorption of lamivudine and enhances the bioavailability of tenofovir (see section 5.2).

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

Animal studies do not indicate direct or indirect harmful effects of tenofovir disoproxil or lamivudine with respect to reproductive toxicity (see section 5.3). The safety of tenofovir in human pregnancy has not been fully established. However, sufficient numbers of first trimester exposures have been monitored to detect at least a twofold increase in the risk of overall birth defects. No increase in birth defects was seen for tenofovir disoproxil or lamivudine (www.apregistry.com/)

Breast-feeding

Lamivudine and tenofovir disoproxil are excreted into the breast milk of lactating mothers. There is insufficient information on the effects of tenofovir in breast-feeding infants.

Current recommendations on HIV/PrEP and breast-feeding (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

Animal studies do not indicate harmful effects of tenofovir disoproxil and lamivudine on fertility. (see section 5.3).

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. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving and operating machinery.

4.8 Undesirable effects

In patients receiving tenofovir disoproxil, rare events of renal impairment, renal failure and uncommon events of 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).

Approximately one third of patients can be 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 adult patients discontinued treatment due to the gastrointestinal events.

The adverse reactions considered related to tenofovir disoproxil and lamivudine are listed below by body system, organ class and absolute frequency. 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).

Blood and lymphatic system disorders
Uncommon: neutropenia and anaemia (both occasionally severe), thrombocytopenia
Very rare: pure red cell aplasia

Metabolism and nutrition disorders:
Very common: hypophosphataemia[1]
Uncommon: hypokalaemia[1]
Rare: lactic acidosis

Nervous system disorders:
Very common: dizziness
Common: headache, insomnia
Very rare: peripheral neuropathy (or paraesthesia)

Respiratory, thoracic and mediastinal disorders
Common: cough, nasal symptoms
Very rare: dyspnoea

Gastrointestinal disorders:
Very common: diarrhoea, vomiting, nausea
Common: abdominal pain, abdominal distension, flatulence, diarrhoea
Rare: pancreatitis, elevated serum amylases

Hepatobiliary disorders:
Common: increased transaminases
Rare: hepatic steatosis, hepatitis

Skin and subcutaneous tissue disorders:
Very common: rash, alopecia

Rare: angioedema

Musculoskeletal and connective tissue disorders:
Common: arthralgia, muscle 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, malaise, fever

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

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

The following laboratory abnormalities were reported in these trials.

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

	2-4 (< 8.4 mg/dl)	13 (1%)	19 (2%)	28 (2%)	39 (2%)
Neutrophils	1 (1000-1300/mm3)	23 (2%)	25 (2%)	208 (13%)	13 (10%)
	2-4 (< 750 mm3)	7 (<1%)	7 (<1%)	73 (5%)	56 (3%)

a. Grade 1 phosphorus was not reported for the Partners PrEP trial
b. Grading is per DAIDS criteria

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

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

Changes in Bone Mineral Density (BMD)

In clinical trials of HIV-1 uninfected individuals, decreases in BMD were observed. In the iPrEx trial, a substudy of 503 subjects found mean changes from baseline in BMD ranging from -0.4% to -1.0% across total hip, spine, femoral neck, and trochanter in the emtricitabine‡/tenofovir disoproxil fumarate group compared with the placebo group, which returned toward baseline after discontinuation of treatment. Thirteen percent of subjects receiving emtricitabine‡/tenofovir disoproxil fumarate vs. 6% of subjects receiving placebo lost at least 5% of BMD at the spine during treatment. Bone fractures were reported in 1.7% of the emtricitabine‡/tenofovir disoproxil fumarate group compared with 1.4% in the placebo group. No correlation between BMD and fractures was noted (see 5.1 Clinical results). The Partners PrEP trial found similar fracture rates between treatment and placebo groups (0.8% and 0.6%, respectively). No BMD evaluations were conducted during this trial.

Description of selected adverse reactions

Renal toxicity

As 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).

Interaction with didanosine

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

Metabolic parameters

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

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

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).

Special populations

Paediatric population

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

The adverse reactions observed in paediatric patients who received treatment with tenofovir disoproxil or lamivudine as single entities were consistent with those observed in clinical studies in adults.

Reductions in bone mineral density (BMD) have been reported with tenofovir disoproxil 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.

Elderly

Caution should be exercised since elderly patients are more likely to have decreased renal function.

Co-infection with hepatitis B or C

Limited data on patients co-infected with HIV/HBV or HIV/HCV indicate that the adverse reaction profile of emtricitabine* and tenofovir disoproxil in patients co-infected with HIV/HBV or HIV/HCV was similar to that observed in patients infected with HIV without co-infection. However, as would be expected, elevations in AST and ALT occurred more frequently than in the general HIV infected population.

In HIV-negative individuals limited data indicate that the adverse reaction profile of emtricitabine* and tenofovir disoproxil was similar in individuals with and without hepatitis B/C infection.

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).

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 to the marketing authorisation holder, or, if available, via the national reporting system.

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 to the marketing authorisation holder, or, if available, via the national reporting system.

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.

Treatment

Since a negligible amount of lamivudine was removed via (4-hour) haemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous haemodialysis would be clinically beneficial in a lamivudine overdose.

Tenofovir disoproxil can be removed by haemodialysis; the median haemodialysis clearance of tenofovir disoproxil is 134 ml/minute. The elimination of tenofovir disoproxil by peritoneal dialysis has not been studied.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Lamivudine, the negative enantiomer of 2'-deoxy-3'-thiacytidine, is a dideoxynucleoside analogue. Tenofovir disoproxil is converted *in vivo* to tenofovir, a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate.
Lamivudine and tenofovir are phosphorylated by cellular enzymes to form lamivudine triphosphate and tenofovir diphosphate, respectively. Lamivudine triphosphate and tenofovir diphosphate competitively inhibit HIV-1 reverse transcriptase, resulting in DNA chain termination. Both substances are active against HIV-1 and HIV-2, as well as against hepatitis B virus.

Pharmacodynamic effects

Antiviral activity in cell culture

Lamivudine
The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines including monocytes and (PBMCs) using standard susceptibility assays. EC_{50} values were in the range of 0.003 to 15 microM. against HIV-1 clades A-G and group O viruses

Tenofovir disoproxil
The antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in T lymphoblastoid cell lines, primary monocyte/macrophage cells and PBMCs. The EC50 values for tenofovir were in the range of 0.04-8.5 microM. Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC50 values ranged from 0.5-2.2 microM).

Resistance in vitro and in vivo
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. HIV strains which expressed 3 or more TAMs that included either the M41L or L210W mutation showed reduced response to tenofovir.

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

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

Clinical efficacy and safety

Several clinical studies have confirmed the efficacy of the individual components of this fixed dose combination product. Lamivudine and tenofovir disoproxil were used as single entities in different combination regimens. No clinical studies have been conducted.with the combination lamivudine and tenofovir disoproxil.

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

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

In the Partners PrEP trial, conducted in serodiscordant heterosexual couples to evaluate the efficacy and safety of emtricitabine§/tenofovir disoproxil versus placebo, in preventing HIV-1 acquisition by the uninfected partner, the risk reduction for emtricitabine§/tenofovir disoproxil relative to placebo was 75% (HR: 0.25, 95% CI: 0.55-0.87, p=0.005) following 7827 person-years of follow-up.
In a post-hoc case control study of plasma drug levels in about 10% of study subjects, risk reduction appeared to be the greatest in subjects with detectable plasma tenofovir. Efficacy was therefore strongly correlated with adherence.

5.2 Pharmacokinetic properties

The absorption characteristics of [HA414 trade name] have been determined after a single dose administration of [HA414 trade name] consisting of lamivudine/tenofovir disoproxil fumarate 300mg/300mg in healthy volunteers are as follows

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

Pharmacokinetic variable	**Mean value ± Standard deviation (geometric mean)**	
	Lamivudine	**Tenofovir disoproxil fumarate**
Maximum concentration (C_{max})	2.24 µg/ml (±0.69)	312 ng/ml (±68)
Area under the curve (AUC_{0-inf}), a measure of the extent of absorption	10.54 µg.h/ml (±2.94)	2754 ng.h/ml (±586).
Time to attain maximum concentration (T_{max})	2.15 hours (± 0.87).hour	2.06 (± 0.61) hours

Pharmacokinetics of lamivudine and tenofovir disoproxil

	Lamivudine	**Tenofovir disoproxil**
General		
		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.
Absorption		
Absolute bioavailability	NA	NA
Oral bioavailability	80-85%	25%
Food effect	Co-administration of lamivudine with food results in a delay of T_{max} and a lower C_{max} (decreased by 47%). However, the extent (based on the AUC) of lamivudine absorbed is not influenced.	<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>
Distribution		
Volume of distribution (mean)	1.3 L/kg	800 ml/kg
Plasma protein binding *in vitro*	< 36% serum albumin in vitro	< 0.7 % (serum protein binding < 7.2%)
Tissue distribution	mean CSF:serum ratio=0.12. The true extent of penetration or relationship with any clinical efficacy is unknown.	Well distributed, with highest concentrations in kidney and liver.
Metabolism		
	Only minor route (< 10%)	In vitro studies have determined that neither tenofovir disoproxil nor tenofovir is a substrate for the CYP450 enzymes.
Active metabolite(s)	None	Tenofovir
Elimination		
Elimination half life	5-7 h 22 h for intracellular lamivudine triphosphate	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)	0.32 L/h/kg	0.23 L/h/kg
% of dose excreted in urine	> 70% [Predominantly cleared unchanged]	70-80% as unchanged drug
% of dose excreted in faeces	NA	NA
Pharmacokinetic linearity	Linear pharmacokinetics	Linear pharmacokinetics (dose range 75 to 600 mg)
Drug interactions *(in vitro*)		
Transporters	OCT (organic cationic transporters)	Substrate of hOAT 1, hOAT3 and MRP 4.
Metabolizing enzymes		No significant inhibition of CYP3A4, CYP2D6, CYP2C9, CYP2E1, or CYP1A1/2

Special populations

Children

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.

Limited data are available in adolescents receiving a daily dose of 300 mg of lamivudine. Pharmacokinetic parameters are comparable to those reported in adults.

Elderly

Pharmacokinetic data for tenofovir and lamivudine in subjects aged over 65 years are limited.

Renal impairment

[HA414 trade name] is not recommended for use in patients with a creatinine clearance < 50 ml/min, as appropriate dose adjustments are not possible.

Pharmacokinetic parameters of tenofovir disoproxil were determined following administration of a single dose of tenofovir disoproxil 245 mg to 40 non-HIV, non-HBV infected adult patients with varying degrees of renal impairment defined according to baseline creatinine clearance (CrCl) (normal renal function when CrCl > 80 ml/min; mild with CrCl = 50-79 ml/min; moderate with CrCl = 30-49 ml/min and severe with CrCl = 10-29 ml/min). Compared with patients with normal renal function, the mean (%CV) tenofovir exposure increased from 2,185 (12%) ng·h/ml in subjects with CrCl > 80 ml/min to respectively 3,064 (30%) ng·h/ml, 6,009 (42%) ng·h/ml and 15,985 (45%) ng·h/ml in patients with mild, moderate and severe renal impairment. The dosing recommendations in patients with renal impairment, with increased dosing interval, are expected to result in higher peak plasma concentrations and lower C_{min} levels in patients with renal impairment compared with patients with normal renal function. The clinical implications of this are unknown.

In patients with end-stage renal disease (ESRD) (CrCl < 10 ml/min) requiring haemodialysis, between dialysis tenofovir concentrations substantially increased over 48 hours achieving a mean C_{max} of 1,032 ng/ml and a mean AUC_{0-48h} of 42,857 ng·h/ml. It is recommended that the dosing interval for tenofovir disoproxil 245 mg (as fumarate) is modified in adult patients with creatinine clearance < 50 ml/min or in patients who already have ESRD and require dialysis.

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

The pharmacokinetics of tenofovir following a 245 mg single dose of tenofovir disoproxil have been studied in non-HIV infected subjects with moderate to severe (ChildPugh B to C) hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in subjects with hepatic impairment compared with unimpaired subjects.

Gender

There is no evidence that a dose adjustment of tenofovir disoproxil or lamivudine would be required based on the effects of gender on PK parameters.

Ethnicity

There is no evidence that a dose adjustment of tenofovir disoproxil or lamivudine would be required based on the effects of ethnicity on PK parameters.

5.3 Preclinical safety data

Tenofovir disoproxil

Preclinical studies in rats, dogs and monkeys revealed target-organ effects on gastrointestinal tract, kidney, bone and a decrease in serum phosphate concentration. Bone toxicity was diagnosed as osteomalacia (monkeys) and reduced bone mineral density (rats and dogs). Findings in the rat and monkey studies indicated that there was a substance-related decrease in intestinal absorption of phosphate with potential secondary reduction in bone mineral density. However, no conclusion could be drawn on the mechanism(s) underlying these toxicities.

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

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

Tenofovir disoproxil did not show any carcinogenic potential in a long-term oral carcinogenicity study in rats. A long-term oral carcinogenicity study in mice showed a low incidence of duodenal tumours, considered likely related to high local concentration of tenofovir disoproxil in the gastrointestinal tract at a dose of 600 mg/kg/day. While the mechanism of tumour formation is uncertain, the findings are unlikely to be of relevance to humans.

Lamivudine

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet: croscarmellose sodium, lactose monohydrate, magnesium stearate and microcrystalline cellulose.
Film coat: hypromellose, propylene glycol and titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

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

6.5 Nature and contents of container

The primary packs are:
60cc white round HDPE bottle fitted with 33mm white polypropylene screw cap closure with SG-75M liner and containing a molecular sieve desiccant. Pack size: 30 tablets.
250cc white round HDPE bottle fitted with 53mm white polypropylene screw cap with Selig M1 liner and containing molecular sieve desiccant and rayon. Pack size: 100 tablets.
60cc blue HDPE opaque bottle fitted with 33mm blue opaque polypropylene screw cap with SG-100 liner and containing a molecular sieve desiccant. Pack size: 30 tablets.

6.6 Instructions for use and handling and disposal

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

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

7. SUPPLIER

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HA414

9. DATE OF PREQUALIFICATION

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10. DATE OF REVISION OF THE TEXT

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