# 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

[HA417 trade name]*

# 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate (equivalent to 245 mg of tenofovir disoproxil or 136 mg of tenofovir).

Excipients with known effects:

Each tablet contains 136 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

# 3. PHARMACEUTICAL FORM

Blue-coloured, oval-shaped, film-coated tablets debossed with "M117" on one side and plain on the other side.

# 4. CLINICAL PARTICULARS

## 4.1 Therapeutic indications

[HA417 trade name] is indicated in combination with at least one other antiretroviral product for the treatment of HIV-1 infection in adults and adolescents over 10 years of age and weighing at least 30 kg.

[HA417 trade name] may be used in combination with other measures for pre-exposure prophylaxis (PrEP) in adults and adolescents (weighing at least 35 kg) at substantial risk of HIV infection.

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

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

## 4.2 Posology and method of administration

Therapy should be initiated by a healthcare provider experienced in the prevention and management of HIV infection.

Posology

*Adults and adolescents*
The recommended dose of [HA417 trade name] is one tablet (200 mg emtricitabine and 245 mg tenofovir disoproxil), taken orally, once daily with food or between meals.

*Special populations*

*Children and adolescents*
HIV-therapy: [HA417 trade name] should not be used in children under 10 years of age and in adolescents weighing less than 30 kg since appropriate dose adjustments cannot be achieved with this product.

PrEP: [HA417 trade name] should not be used in children under 10 years of age and in adolescents weighing less than 35 kg due to insufficient data on safety and efficacy.

* Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.
† Formerly Matrix Laboratories Limited.

*Elderly*
There is no need for dose adjustment of [HA417 trade name] in the elderly, except if there is evidence of renal impairment (see section 4.4 ).

*Renal impairment*
Emtricitabine and tenofovir are both eliminated by renal excretion. Thus, exposure to both compounds increases in patients with renal dysfunction. The long-term safety of tenofovir and emtricitabine in mild renal impairment (creatinine clearance 50-80 mL/minute) has not been fully assessed. Therefore, in patients with renal impairment [HA417 trade name] should only be used if the potential benefits of treatment are considered to outweigh the potential risks. Patients with renal impairment may require close monitoring of renal function (see section 4.4). Dose interval adjustments are recommended for patients with creatinine clearance between 30 and 49 mL/minute. These dose adjustments have not been confirmed in clinical studies and the clinical response to treatment should be closely monitored in such patients (see sections 4.4 and 5.2).

*Mild renal impairment (creatinine clearance 50-80 mL/minute):* Limited data from clinical studies support once daily dosing of [HA417 trade name] in patients with mild renal impairment (see section 4.4).

*Moderate renal impairment (creatinine clearance 30-49 mL/minute):*
[HA417 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 [HA417 trade name] every 48 hours is recommended, based on modelling of single-dose pharmacokinetic data for emtricitabine and tenofovir disoproxil in non-HIV infected subjects with varying degrees of renal impairment (see section 4.4).

*Severe renal impairment (creatinine clearance < 30 mL/minute) and haemodialysis patients:* [HA417 trade name] is not recommended for patients with severe renal impairment (creatinine clearance < 30 mL/minute) and in patients who require haemodialysis because appropriate reductions cannot be achieved with the combination tablet.

<u>*Paediatrics with renal impairment:*</u>
Not recommended for use in individuals under the age of 18 years with renal impairment (see section 4.4).

*Hepatic impairment*
The pharmacokinetics of tenofovir disoproxil has been studied in patients with hepatic impairment. No dose adjustment is required for tenofovir disoproxil in these patients. The pharmacokinetics of emtricitabine has not been studied in patients with hepatic impairment. Based on minimal hepatic metabolism and the renal route of elimination for emtricitabine, it is unlikely that a dose adjustment would be required for [HA417 trade name] in patients with hepatic impairment (see sections 4.4 and 5.2).

*Discontinuation of therapy*
Where discontinuation of therapy of HIV-1 infection with one of the components of [HA417 trade name] is indicated or where dose modification is necessary, separate preparations of emtricitabine and tenofovir disoproxil should be used.

If [HA417 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).
Individuals who wish to discontinue oral PrEP should be advised to continue PrEP dosing for at least 4 weeks after the last potential HIV exposure.

*Advice on missed dose*
If a dose of [HA417 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 [HA417 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 [HA417 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 [HA417 trade name].

***Method of administration***

[HA417 trade name] should be swallowed whole.

Alternatively, 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 of the excipients listed in section 6.1.

## 4.4 Special warnings and precautions for use

*General*

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

*Pre-exposure prophylaxis (PrEP)*

Comprehensive management to reduce the risk of acquiring HIV-1:

Emtricitabine and tenofovir disoproxil should be used for pre-exposure prophylaxis only as part of a comprehensive prevention strategy that includes other prevention measures, such as safer sex practices, because pre-exposure prophylaxis is not always effective in preventing the acquisition of HIV-1 (see section 5.1).

Uninfected individuals should be counselled about safer sex practices that include consistent and correct use of condoms, knowledge of their HIV-1 status and that of their partner(s), and regular testing for other sexually transmitted infections that can facilitate HIV-1 transmission (such as syphilis and gonorrhoea).

Only an individual who has been confirmed HIV-negative should use [HA417 trade name] to reduce the risk of acquiring HIV-1. HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking only emtricitabine and tenofovir disoproxil, because these do not constitute a complete treatment regimen for HIV-1. Therefore, care should be taken to minimize drug exposure in HIV-infected individuals.

Many HIV-1 tests, such as rapid tests, detect anti-HIV antibodies and may not identify HIV-1 during the acute stage of infection. Prior to initiating emtricitabine and tenofovir disoproxil for pre-exposure prophylaxis, 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 sex, or condom broke during sex with an HIV-1 infected partner) that may have occurred within the last month.

If clinical symptoms consistent with acute viral infection are present and recent (<1 month) HIV-exposure is suspected, starting PrEP should be delayed for at least one month. HIV-1 status should be then reconfirmed using a reliable test as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection.

While using emtricitabine and tenofovir disoproxil for PrEP, HIV-1 screening tests should be repeated at least every 3 months. If symptoms consistent with acute HIV-1 infection develop following a potential exposure event, PrEP should be discontinued until negative infection status is confirmed using a reliable test as an aid in the diagnosis of HIV-1, including acute or primary HIV-1 infection.

Uninfected individuals should be counselled to strictly adhere to the recommended emtricitabine and tenofovir disoproxil dosing schedule. The effectiveness of emtricitabine and tenofovir disoproxil in reducing the risk of acquiring HIV-1 is strongly correlated with adherence as demonstrated by measurable drug levels in clinical trials.

An assessment of the risk for HIV-1 acquisition should be done at each visit.

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.
As with post-exposure prophylaxis, PrEP may be discontinued 28 days after the last potential exposure to HIV if people do not have continuing substantial risk for acquiring HIV.

*HIV-therapy*

Patients using emtricitabine and tenofovir disoproxil should be advised that antiretroviral therapy has not been proven to prevent fully the risk of transmission of HIV to others through sexual contact or contamination with blood. Appropriate precautions must continue to be taken.

Co-administration of other medicinal products

Emtricitabine and tenofovir disoproxil should not be administered concomitantly with other medicinal products containing emtricitabine, tenofovir disoproxil (e.g. as fumarate, phosphate or succinate), tenofovir alafenamide or other cytidine analogues, such as lamivudine (see below and section 4.5). Emtricitabine and tenofovir disoproxil should not be administered concomitantly with adefovir dipivoxil.

Triple nucleoside therapy: There have been reports of a high rate of virological failure and of emergence of resistance at an early stage when tenofovir disoproxil was combined with lamivudine and abacavir as well as with lamivudine and didanosine. Lamivudine and emtricitabine are similar in structure, pharmacokinetics and pharmacodynamics. Therefore, the same problems may be seen if emtricitabine and tenofovir disoproxil is administered with a third nucleoside analogue.

Co-administration of tenofovir disoproxil and didanosine is not recommended.
This co-administration may increase the risk of didanosine-related adverse events. Rare cases of pancreatitis and lactic acidosis, sometimes fatal, have been reported. 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 leading to cytotoxic effects. A decreased dosage of 250 mg didanosine co-administered with tenofovir disoproxil has been associated with reports of high rates of virological failure within several tested combinations for the treatment of HIV-1 infection.

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 (ritonavir or cobicistat).

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 Impairment*

Emtricitabine and tenofovir disoproxil are primarily excreted by the kidneys, through a combination of glomerular filtration and active tubular secretion. Renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir disoproxil in clinical practice (see section 4.8). It is recommended that creatinine clearance/estimated glomerular function be calculated in all individuals prior to initiating therapy and as clinically appropriate during therapy with emtricitabine and tenofovir disoproxil.

Use of tenofovir disoproxil should be avoided with concurrent 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 or interleukin-2). If concomitant use of tenofovir disoproxil and nephrotoxic agents is unavoidable, renal function should be monitored weekly.

HIV-therapy
If the creatinine test is routinely available, use the estimated glomerular filtration rate at baseline before initiating tenofovir disoproxil-containing regimens.
Benefits and risks should be carefully weighed when initiating tenofovir disoproxil in patients at increased risk for renal toxicity, i.e. patients with an estimated glomerular filtration rate <50 ml/min, more than 50 years of age, with low body weight (<50 kg), diabetes, uncontrolled hypertension, renal failure, or concomitant use of boosted PIs or nephrotoxic drugs (see section 4.2).
Creatinine testing during therapy is particularly advisable for high-risk patients to detect and limit further progression of renal impairment. If available, also serum phosphate should be measured in these patients.
If serum phosphate is < 1.5 mg/dl (0.48 mmol/l) or creatinine clearance is decreased to < 50 ml/min in any patient receiving emtricitabine and tenofovir disoproxil, renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations (see section 4.8, proximal tubulopathy).
Consideration should also be given to interrupting treatment with tenofovir disoproxil in patients with creatinine clearance decreased to < 50 ml/min or decreases in serum phosphate below 1.0 mg/dl (0.32 mmol/l). Interrupting treatment with emtricitabine and tenofovir disoproxil should also be considered in case of progressive decline of renal function when no other cause has been identified.

The renal safety of tenofovir disoproxil taken together with emtricitabine has only been studied to a very limited degree in patients with impaired renal function (creatinine clearance < 80 ml/min). Dose interval adjustments are recommended for patients with creatinine clearance 30-49 ml/min (see section 4.2). Limited clinical study data suggest that the prolonged dose interval is not optimal and could result in increased toxicity and possibly inadequate response. Furthermore, in a small clinical study, a subgroup of patients with creatinine clearance between 50 and 60 ml/min who received tenofovir disoproxil in combination with emtricitabine every 24 hours had a 2-4-fold higher exposure to tenofovir and worsening of renal function (see section 5.2). Therefore, a careful benefit-risk assessment is needed when emtricitabine and tenofovir disoproxil is used in patients with creatinine clearance < 60 ml/min, and renal function should be closely monitored. In addition, the clinical response to treatment should be closely monitored in patients receiving emticitabine and tenofovir disoproxil at a prolonged dosing interval. The use of this medicine is not recommended in patients with severe renal impairment (creatinine clearance < 30 ml/min) and in patients who require haemodialysis.

Pre-exposure Prophylaxis (PrEP)
Emtricitabine and tenofovir disoproxil should not be used for PrEP in HIV-1 uninfected individuals with estimated creatinine clearance below 60 ml/min. Creatinine testing should be undertaken quarterly during the first 12 months and annually thereafter. If a decrease in estimated creatinine clearance is observed in uninfected individuals while using this medicine for PrEP, potential causes should be evaluated and potential risks and benefits of continued use re-assessed.

The use of [HA417 trade name] is not recommended in individuals under the age of 18 years with renal impairment (see section 4.2). [HA417 trade name] should not be initiated in paediatric patients with renal impairment and should be discontinued in paediatric patients who develop renal impairment during [HA417 trade name] use.

*Bone effects*

HIV-therapy
In a controlled clinical study in adults decreases in bone mineral density of spine and changes in bone biomarkers from baseline were observed in both treatment groups, but were significantly greater in the tenofovir disoproxil treatment group than in the comparator group treated with stavudine (each in combination with lamivudine and efavirenz) at 144 weeks. Decreases in bone mineral density of the hip were

significantly greater in this group until 96 weeks. However, there was no increased risk of fractures or evidence for clinically relevant bone abnormalities over 144 weeks.
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, [HA417 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.

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

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

Patients with chronic hepatitis B or C treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. Physicians should refer to current treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV). In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant Summary of Product Characteristics for these medicinal products.
The safety and efficacy of emtricitabine and tenofovir disoproxil have not been established for the treatment of chronic HBV infection. Emtricitabine and tenofovir individually and in combination have shown activity against HBV (see section 5.1). Limited clinical experience suggests that emtricitabine and tenofovir disoproxil have anti-HBV activity when used in antiretroviral combination therapy to control HIV infection.

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

*Liver disease*

The safety and efficacy of emtricitabine and tenofovir disoproxil have not been established in patients with significant underlying liver disorders (see also sections 4.2 and 5.2.). Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy (CART) and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

*Weight and metabolic parameters*

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

*Mitochondrial toxicity*

Nucleos(t)ide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV

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

*Immune Reactivation Syndrome*

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

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillan-Barré syndrome) 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.

HIV infected patients co-infected with hepatitis B virus may experience acute exacerbations of hepatitis associated with immune reactivation syndrome following the initiation of antiretroviral therapy.

*Osteonecrosis*

Osteonecrosis has been reported particularly in patients with advanced HIV-disease and/or long-term exposure to CART. Its 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.

*Opportunistic infections*

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

*Elderly*

The combination of emtricitabine and tenofovir disoproxil has not been studied in patients over the age of 65. Elderly patients are more likely to have decreased renal function. Therefore caution should be exercised when treating elderly patients with emtricitabine and tenofovir disoproxil.

*Excipients*

[HA417 trade name] contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption may experience symptoms of intolerance when using it.

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

As [HA417 trade name] contains emtricitabine and tenofovir disoproxil, any interactions that have been identified with these agents individually may occur with this fixed dose combination.

Interaction studies have only been performed in healthy adult volunteers.

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

*In vitro* and clinical pharmacokinetic interaction studies have shown the potential for cytochrome P450 mediated interactions involving emtricitabine and tenofovir disoproxil with other medicinal products is low.

*Concomitant use not recommended*
[HA417 trade name] should not be administered with any other medicinal products containing tenofovir disoproxil, e.g. as fumarate, phosphate or succinate, tenofovir alafenamide, adefovir dipivoxil, emtricitabine or lamivudine (see section 4.4 and below).

*Interactions relevant to emtricitabine*

*In vitro*, emtricitabine did not inhibit metabolism mediated by any of the following human CYP450 isoforms: 1A2, 2A6, 2B6, 2C9, 2C19, 2D6 and 3A4, and did not inhibit enzymatic glucuronidation.

There are no clinically significant interactions when emtricitabine is co-administered with indinavir, zidovudine, stavudine, famciclovir or tenofovir. Emtricitabine is primarily excreted via glomerular filtration and active tubular secretion. With the exception of famciclovir and tenofovir disoproxil, the effect of co-administration of emtricitabine with medicinal products that are excreted by the renal route, or other medicinal products known to affect renal function, has not been evaluated.

Co-administration of [HA417 trade name] with medicinal products that reduce renal function or are eliminated by active tubular secretion may lead to an increase in serum concentrations of either emtricitabine or a co-administered medicinal product due to competition for this elimination pathway.
Use of [HA417 trade name] should be avoided with concurrent or recent use of a nephrotoxic medicinal product. Some examples include, but are not limited to aminoglycosides, amphotericin B, foscarnet, aciclovir, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2 and high-dose or multiple non-steroidal anti-inflammatory drugs. There is no clinical experience or virologic rationale for the co-administration of emtricitabine and cytidine analogues. Consequently, [HA417 trade name] should not be administered in combination with lamivudine for the treatment of HIV infection (see section 4.4).

*Interactions relevant to tenofovir disoproxil*

Didanosine
Co-administration of [HA417 trade name] and didanosine is not recommended (see section 4.4 and Table 2).

Renally eliminated medicinal products
Since tenofovir is primarily eliminated by the kidneys, co-administration of [HA417 trade name] with medicinal products that reduce renal function or compete for active tubular secretion via transport proteins hOAT 1, hOAT 3 or MRP 4 (e.g. cidofovir) may increase serum concentrations of tenofovir and/or the co-administered medicinal products.

Use of [HA417 trade name] should be avoided with concurrent use of a nephrotoxic medicinal product. Some examples include aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2 (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 Table 1 below (increased exposure is indicated as "↑", decreased exposure as "↓", no change as "↔", twice daily as "b.i.d.", and once daily as "q.d.").

Table 2: 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 concerning co-administration with [HA417 trade name]** |
|---|---|---|
| ANTI-INFECTIVES | | |
| Antiretrovirals | | |
| Protease inhibitors | | |
| Atazanavir (400 mg q.d.) | Atazanavir: AUC: ↓ 25% $C_{max}$: ↓ 21% $C_{min}$: ↓ 40% Tenofovir: AUC: ↑ 24% $C_{max}$: ↑ 14% $C_{min}$: ↑ 22% | If atazanavir and [HA417 trade name]are coadministered, atazanavir should be given at the dose 300 mg q.d. together with ritonavir 100 mg q.d. ("ritonavir-boosting", see below) |
| Atazanavir/ritonavir (300 mg q.d./100 mg q.d.) | Atazanavir: AUC: ↓ 25% $C_{max}$: ↓ 28% $C_{min}$: ↓ 26% Tenofovir: AUC: ↑ 37% $C_{max}$: ↑ 34% $C_{min}$: ↑ 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 (400/100 mg b.i.d.) | Lopinavir/ritonavir: No significant effect on lopinavir/ritonavir PK 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 (300/100 mg b.i.d.) | Darunavir: No significant effect on darunavir/ritonavir PK 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). |

| **Medicinal products by therapeutic areas (dose in mg)** | **Effects on drug levels Mean % change in AUC, Cmax, Cmin** | **Recommendation concerning co-administration with [HA417 trade name]** |
|---|---|---|
| NRTIs | | |
| Didanosine (400 mg q.d.) | Didanosine AUC ↑ 40-60% | The risk of didanosine-related adverse effects (e.g., pancreatitis, lactic acidosis appears to be increased, and CD4 cells may decrease significantly on co-administration. Didanosine at 250 mg co-administered with tenofovir disoproxil within several different antiretroviral combination regimens has been associated with a high rate of virological failure. Co-administration of [HA417 trade name] and didanosine is not recommended (see section 4.4). |
| Hepatitis B virus (HBV) antiviral agents | | |
| Entecavir (1 mg q.d.) | AUC: ↔<br>$C_{max}$: ↔ | No clinically significant pharmacokinetic interactions when tenofovir disoproxil was co-administered with entecavir. |
| Hepatitis C virus (HCV) antiviral agents | | |
| Ledipasvir/sofosbuvir (90 mg/400 mg q.d.) + /Atazanavir/ritonavir (300 mg q.d./100 mg q.d.) + | Ledipasvir:<br>AUC: ↑ 96%<br>Cmax: ↑ 68%<br>Cmin: ↑ 118%<br><br>Sofosbuvir:<br>AUC: ↔<br>Cmax: ↔<br>GS-3310072 (predominating metabolite of sofosbuvir):<br>AUC: ↔<br>Cmax: ↔<br>Cmin: ↑ 42%<br><br>Atazanavir:<br>AUC: ↔<br>Cmax: ↔<br>Cmin: ↑ 63%<br><br>Ritonavir:<br>AUC: ↔<br>Cmax: ↔<br>Cmin: ↑ 45%<br><br>Emtricitabine: ↔<br><br>Tenofovir:<br>AUC: ↔<br>Cmax: ↑ 47%<br>Cmin: ↑ 47% | 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 or cobicistat) has not been established.<br><br>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.) | Ledipasvir: ↔<br><br>Sofosbuvir:<br>AUC: ↓ 27%<br>Cmax: ↓ 37% | Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, ledipasvir/sofosbuvir and darunavir/ritonavir may |

| **Medicinal products by therapeutic areas (dose in mg)** | **Effects on drug levels Mean % change in AUC, Cmax, Cmin** | **Recommendation concerning co-administration with [HA417 trade name]** |
|---|---|---|
| | GS-3310072: ↔<br><br>Darunavir: ↔<br><br>Ritonavir:<br>AUC: ↔<br>Cmax: ↔<br>Cmin: ↑ 48%<br><br>Emtricitabine: ↔<br><br>Tenofovir:<br>AUC: ↑ 50%<br>Cmax: ↑ 64%<br>Cmin: ↑ 59% | 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 or cobicistat) has not been established.<br><br>The combination should be used with caution with frequent renal monitoring, if other alternatives are not available (see section 4.4) |
| Ledipasvir/sofosbuvir<br>(90 mg/400 mg q.d.)<br>/Efavirenz/emtricitabine/tenofovir disoproxil<br>(600 mg/200 mg/245mg q.d.) | Ledipasvir:<br>AUC: ↓ 34%<br>Cmax: ↓ 34%<br>Cmin: ↓ 34%<br><br>Sofosbuvir: ↔<br>GS-3310072:↔<br><br>Efavirenz: ↔<br><br>Emtricitabine: ↔<br><br>Tenofovir:<br>AUC: ↑ 98%<br>Cmax: ↑ 79%<br>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<br>(90 mg/400 mg q.d.)<br>/Emtricitabine/rilpivirine/tenofovir disoproxil<br>(200 mg/25 mg/245mg q.d.) | Ledipasvir: ↔<br><br>Sofosbuvir: ↔<br>GS-3310072: ↔<br><br>Emtricitabine:↔<br><br>Rilpivirine: ↔<br><br>Tenofovir:<br>AUC: ↑ 40%<br>Cmax: ↔<br>Cmin: ↑ 91% | 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.) + Dolutegravir (50 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.) | Sofosbuvir: ↔<br>GS-3310072: ↔<br><br>Ledipasvir: ↔<br><br>Dolutegravir: ↔<br>Emtricitabine:↔<br><br>Tenofovir:<br>AUC: ↑ 65% (↑ 59 to ↑ 71)<br>Cmax: ↑ 61% (↑ 51 to ↑ 72) | No dose adjustment is required. 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 concerning co-administration with [HA417 trade name] |
|---|---|---|
| | Cmin: ↑ 115% (↑ 105 to ↑ 126) | |
| 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:↔<br>GS-331007[2]:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↑ 42% (↑ 37 to ↑ 49)<br><br>Velpatasvir:<br>AUC: ↑ 142% (↑ 123 to ↑ 164)<br>$C_{max}$: ↑ 55% (↑ 41 to ↑ 71)<br>$C_{min}$: ↑ 301% (↑ 257 to ↑ 350)<br><br>Atazanavir:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↑ 39% (↑ 20 to ↑ 61)<br><br>Ritonavir:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↑ 29% (↑ 15 to ↑ 44)<br><br>Emtricitabine:↔<br><br>Tenofovir:<br>AUC: ↔<br>$C_{max}$: ↑ 55% (↑ 43 to ↑ 68)<br>$C_{min}$: ↑ 39% (↑ 31 to ↑ 48) | 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 or cobicistat) has not been established.<br>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:<br>AUC: ↓ 28% (↓ 34 to ↓ 20)<br>$C_{max}$: ↓ 38% (↓ 46 to ↓ 29)<br>GS-331007[2]: ↔<br><br>Velpatasvir:<br>AUC: ↔<br>$C_{max}$: ↓ 24% (↓ 35 to ↓ 11)<br>$C_{min}$: ↔<br><br>Darunavir: ↔<br><br>Ritonavir:↔<br><br>Emtricitabine: ↔<br><br>Tenofovir:<br>AUC: ↑ 39% (↑ 33 to ↑ 44)<br>$C_{max}$: ↑ 55% (↑ 45 to ↑ 66)<br>$C_{min}$: ↑ 52% (↑ 45 to ↑ 59) | 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 or cobicistat) has not been established.<br>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.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.) | Sofosbuvir:<br>AUC: ↓ 29% (↓ 36 to ↓ 22)<br>$C_{max}$: ↓ 41% (↓ 51 to ↓ 29)<br>GS-331007[2]: ↔<br><br>Velpatasvir:<br>AUC: ↔ | Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, sofosbuvir/velpatasvir and lopinavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal |

| Medicinal products by therapeutic areas (dose in mg) | Effects on drug levels Mean % change in AUC, Cmax, Cmin | Recommendation concerning co-administration with [HA417 trade name] |
|---|---|---|
| | $C_{max}$: ↓ 30% (↓ 41 to ↓ 17)<br>$C_{min}$: ↑ 63% (↑ 43 to ↑ 85)<br><br>Lopinavir: ↔<br><br>Ritonavir:↔<br><br>Emtricitabine: ↔<br><br>Tenofovir:<br>AUC: ↔<br>$C_{max}$: ↑ 42% (↑ 27 to ↑ 57)<br>$C_{min}$: ↔ | disorders. The safety of tenofovir disoproxil when used with sofosbuvir/velpatasvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established.<br>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:↔<br>GS-331007[2]:↔<br><br>Velpatasvir:↔<br><br>Raltegravir:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↓ 21% (↓ 58 to ↑ 48)<br><br>Emtricitabine:↔<br><br>Tenofovir:<br>AUC: ↑ 40% (↑ 34 to ↑ 45)<br>$C_{max}$: ↑ 46% (↑ 39 to ↑ 54)<br>$C_{min}$: ↑ 70% (↑ 61 to ↑ 79) | No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4). |
| Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Efavirenz/Emtricitabine/Tenofovir disoproxil (600 mg/200 mg/245 mg q.d.) | Sofosbuvir:<br>AUC: ↔<br>$C_{max}$: ↑ 38% (↑ 14 to ↑ 67)<br>GS-331007[2]:↔<br><br>Velpatasvir:<br>AUC: ↓ 53% (↓ 61 to ↓ 43)<br>$C_{max}$: ↓ 47% (↓ 57 to ↓ 36)<br>$C_{min}$: ↓ 57% (↓ 64 to ↓ 48)<br><br>Efavirenz:↔<br><br>Emtricitabine:↔<br><br>Tenofovir:<br>AUC: ↑ 81% (↑ 68 to ↑ 94)<br>$C_{max}$: ↑ 77% (↑ 53 to ↑ 104)<br>$C_{min}$: ↑ 121% (↑ 100 to ↑ 143) | 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:↔<br>GS-331007[2]:↔<br><br>Velpatasvir:↔<br><br>Emtricitabine:↔<br><br>Rilpivirine:↔ | 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 concerning co-administration with [HA417 trade name]** |
|---|---|---|
| | Tenofovir:<br>AUC: ↑ 40% (↑ 34 to ↑ 46)<br>$C_{max}$: ↑ 44% (↑ 33 to ↑ 55)<br>$C_{min}$: ↑ 84% (↑ 76 to ↑ 92) | |
| 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/Tenofovirdisoproxil (200 mg/245 mg q.d.) | Sofosbuvir:<br>AUC: ↔<br>$C_{max}$: ↓ 30%<br>$C_{min}$: N/A<br>GS-331007[2]:↔<br><br>Velpatasvir:↔<br><br>Voxilaprevir:<br>AUC: ↑ 143%<br>$C_{max}$:↑ 72%<br>$C_{min}$: ↑ 300%<br><br>Darunavir:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↓ 34%<br><br>Ritonavir:<br>AUC: ↑ 45%<br>$C_{max}$: ↑ 60%<br>$C_{min}$: ↔<br><br>Emtricitabine:↔<br><br>Tenofovir:<br>AUC: ↑ 39%<br>$C_{max}$: ↑ 48%<br>$C_{min}$: ↑ 47% | Increased plasma concentrations of tenofovir resulting from co-administration 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 or cobicistat) has not been established.<br>The combination should be used with caution with frequent renal monitoring (see section 4.4). |
| Sofosbuvir<br>(400 mg q.d.)<br>/Efavirenz/Emtricitabine/Tenofovir disoproxil<br>(600 mg/200 mg/245mg q.d.) | Sofosbuvir:<br>AUC: ↔<br>Cmax: ↓ 19%<br>GS-3310072:<br>AUC: ↔<br>Cmax: ↓ 23%<br><br>Efavirenz: ↔<br><br>Emtricitabine: ↔<br><br>Tenofovir:<br>AUC: ↔<br>Cmax: ↑ 25%<br>Cmin: ↔ | No dose adjustment is required. |

*Studies conducted with other medicinal products:* 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/ethinyloestradiol.

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

## 4.6 Fertility, pregnancy and breastfeeding

*Pregnancy*

Animal studies do not indicate reproductive toxicity of tenofovir disoproxil or emtricitabine (see section 5.3). Sufficient numbers of first trimester exposures have been monitored to detect at least a twofold increase in the risk of overall birth defects. No increase in birth defects was seen (www.apregistry.com).

The use of [HA417 trade name] may be considered during pregnancy.

*Breastfeeding*

Emtricitabine and tenofovir have been shown to be excreted in human milk. There is insufficient information on the effects of emtricitabine and tenofovir in newborns/infants.

A risk to the suckling child cannot be excluded.

Current recommendations on HIV and breastfeeding (e.g. those from the WHO) should be consulted before advising patients on this matter. Preferred options may vary depending on the local circumstances.

*Fertility*

Clinical data on the effect of tenofovir disoproxil on fertility are limited.

Animal studies do not indicate harmful effects of emtricitabine and 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, patients should be informed that dizziness has been reported during treatment with emtricitabine and tenofovir disoproxil.

## 4.8 Undesirable effects

HIV-therapy

In a trial for treatment of HIV infection, the most frequently reported adverse reactions considered possibly or probably related to emtricitabine and/or tenofovir disoproxil were nausea (12%) and diarrhoea (7%). The safety profile of emtricitabine and tenofovir disoproxil in this study was consistent with the previous experience with these agents when each was administered with other antiretroviral agents.

In patients receiving tenofovir disoproxil, rare events of renal impairment, renal failure and proximal renal tubulopathy (including Fanconi syndrome) sometimes leading to bone abnormalities (infrequently contributing to fractures) have been reported. Monitoring of renal function is recommended for patients receiving [HA417 trade name] (see section 4.4).

Co-administration of tenofovir disoproxil and didanosine is not recommended as this may result in an increased risk of adverse reactions (see section 4.5). Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported (see section 4.4).

Discontinuation of [HA417 trade name] therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis (see section 4.4).

The adverse reactions considered at least possibly related to treatment with the components of [HA417 trade name] from clinical trial and post-marketing experience 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), common (≥ 1/100, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥ 1/10,000, < 1/1,000) or very rare (< 1/10,000) including isolated reports, or not known (identified through post-marketing safety surveillance and the frequency cannot be estimated from the available data).

*Blood and lymphatic system disorders:*
Common: neutropenia
Uncommon: anaemia

*Immune system disorders:*
Common: allergic reaction

*Metabolism and nutrition disorders:*
Very common: hypophosphataemia
Common: hyperglycaemia, hypertriglyceridaemia
Uncommon: hypokalaemia
Rare: lactic acidosis

*Psychiatric disorders:*
Common: insomnia, abnormal dreams

*Nervous system disorders:*
Very common: headache, dizziness

*Respiratory, thoracic and mediastinal disorders:*
Very rare: dyspnoea

*Gastrointestinal disorders:*
Very common: diarrhoea, vomiting, nausea
Common: elevated serum lipase, elevated amylase including elevated pancreatic amylase, abdominal pain, dyspepsia, flatulence
Uncommon: pancreatitis

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

*Skin and subcutaneous tissue disorders:*
Very common: rash
Common: urticaria, vesiculobullous rash, pustular rash, maculopapular rash, pruritus and skin discolouration
Uncommon: angioedema

*Musculoskeletal and connective tissue disorders:*
Very common: elevated creatine kinase
Uncommon: rhabdomyolysis, muscular weakness
Rare: osteomalacia (manifested as bone pain and infrequently contributing to fractures), myopathy

*Renal and urinary disorders:*
Uncommon: increased creatinine, proteinuria, proximal renal tubulopathy including Fanconi syndrome
Rare: renal failure (acute and chronic), acute tubular necrosis, nephritis (including acute interstitial nephritis), nephrogenic diabetes insipidus

*General disorders and administration site conditions:*
Very common: asthenia
Common: pain
Not known: Immune reconstitution syndrome

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 no new adverse reactions were reported. Of those reactions, occurring in at least 2% of subjects, the following were reported more frequently in the treatment group (as compared to placebo, all from iPrEx-trial).

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

The following laboratory abnormalities were reported in these trials.

| | Grade[b] | iPrEx Trial | | Partners PrEP Trial | |
|---|---|---|---|---|---|
| | | FTC/TDF N=1251 | Placebo N=1248 | FTC/TDF N=1579 | Placebo N=1548 |
| Creatinine | 1 (1.1-1.3 x ULN | 27 (2%) | 21 (2%) | 18 (1%) | 12 (<1%) |
| | 2-4 (>1.4 x ULN | 5 (<1%) | 3 (<1%) | 2 (<1%) | 1 (<1%) |
| Phosphorus | 1 (2.5 - <LLN mg/dl | 81 /7%) | 110 (9%) | NR[a] | NR[a] |
| | 2-4 (<2.5 mg/dl | 123 (10%) | 101 (8%) | 140 (9%) | 136 (9%) |
| AST | 1 (1.25 - <2.5 x ULN) | 175 (14%) | 175 (14%) | 20 (1%) | 25 (2%) |
| | 2-4 (> 2.6 x ULN) | 57 (5%) | 61 (5%) | 10 (<1%) | 4 (<1%) |
| ALT | 1 (1.25 - <2.5 x ULN) | 178 (14%) | 194 (16%) | 21 (1%) | 25 (2%) |
| | 2-4 (> 2.6 x ULN) | 84 (7%) | 82 (7%) | 4 (<1%) | 6 (<1%) |
| Haemoglobin | 1 (8.5-10 mg/dl) | 49 (4%) | 62 (5%) | 56 (4%) | 39 (2%) |
| | 2-4 (< 8.4 mg/dl) | 13 (1%) | 19 (2%) | 28 (2%) | 39 (2%) |
| Neutrophils | 1 (1000-1300/$mm^3$) | 23 (2%) | 25 (2%) | 208 (13%) | 153 (10%) |
| | 2-4 (< 750 $mm^3$) | 7 (<1%) | 7 (<1%) | 73 (5%) | 56 (3%) |

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

In addition to the laboratory abnormalities described above, grade 1 proteinuria occurred in 6% of subjects receiving emtricitabine/tenofovir disoproxil in the iPrEx trial. Grades 2-3 proteinuria and glycosuria occurred in less than 1% of subjects treated with emtricitabine/tenofovir disoproxil 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 sub-study 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 group compared with the placebo group, which returned toward baseline after discontinuation of treatment. Thirteen percent of subjects receiving emtricitabine/tenofovir disoproxil 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 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 impairment*
As [HA417 trade name] may cause renal damage, monitoring of renal function is recommended (see sections 4.4 and 4.8). Proximal renal tubulopathy generally resolved or improved after tenofovir disoproxil discontinuation. However, in some patients, declines in creatinine clearance did not completely resolve despite tenofovir disoproxil discontinuation. Patients at risk of renal impairment (such as patients with baseline renal risk factors, advanced HIV disease, or patients receiving concomitant nephrotoxic medications) are at increased risk of experiencing incomplete recovery of renal function despite tenofovir disoproxil discontinuation (see section 4.4).
The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), hypokalaemia, muscular weakness, myopathy and hypophosphataemia. These events are not likely to be causally associated with tenofovir disoproxil therapy in the absence of proximal renal tubulopathy.

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

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

*Immune Reactivation Syndrome*
In HIV-infected patients with severe immune deficiency at the time of initiation of CART, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease) have also been reported; the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

*Osteonecrosis*
Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to CART. The frequency of this is unknown (see section 4.4).

Paediatric population

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

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

Other special population(s)

*Elderly*
Emtricitabine/tenofovir disoproxil has not been studied in patients over the age of 65. Elderly patients are more likely to have decreased renal function, therefore caution should be exercised when treating elderly patients with [HA417 trade name].

*HIV/HBV or HCV co-infected patients*
Only a limited number of patients were co-infected with HBV (n=13) or HCV (n=26) in the abovementioned study. 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 it would be expected, elevations in AST and ALT occurred more frequently than in the general HIV infected population.
In HIV-negative individuals limited data indicate that the adverse reaction profile of emtricitabine and tenofovir disoproxil was similar in individuals with and without hepatitis B/C infection.

***Reporting of suspected adverse reactions***

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

### 4.9 Overdose

If overdose occurs the patient must be monitored for evidence of toxicity (see section 4.8), and standard supportive treatment applied as necessary.
Up to 30% of the emtricitabine dose and approximately 10% of the tenofovir can be removed by haemodialysis. It is not known whether emtricitabine or tenofovir can be removed by peritoneal dialysis.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

*Pharmacotherapeutic group:* Antiviral for systemic use; antivirals for treatment of HIV infection, combinations. ATC code: J05AR03

*Mechanism of action and pharmacodynamic effects*

Emtricitabine is an analogue of the nucleoside cytidine. Tenofovir disoproxil is converted *in vivo* to tenofovir, a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate. Emtricitabine and tenofovir are phosphorylated by cellular enzymes to form emtricitabine triphosphate and tenofovir diphosphate, respectively. Emtricitabine triphosphate and tenofovir diphosphate competitively inhibit HIV-1 reverse transcriptase (RT), resulting in DNA chain termination. Both substances are active against HIV-1 and HIV-2, as well as against hepatitis B virus.

Clinical results:

*HIV therapy*

When tenofovir and emtricitabine were combined with efavirenz in treatment-naïve patients with HIV, the proportion of patients (ITT) with HIV-RNA <50 copies/ml were 80 and 64% at 48 and 144 weeks, respectively. In another study, were tenofovir and emtricitabine were combined with lopinavir/ritonavir given once or twice daily in treatment naive patients, 70% and 64% of patients demonstrated HIV-1 RNA <50 copies/ml with the once and twice daily regimens of lopinavir/ritonavir, respectively.

*Pre-exposure Prophylaxis*

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

Limited clinical experience in patients co-infected with HIV and HBV suggests that treatment with emtricitabine or tenofovir disoproxil in antiretroviral combination therapy to control HIV infection also results in a reduction in HBV DNA (3 log10 reduction or 4 to 5 log10 reduction, respectively) (see section 4.4).

*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. In addition, a K70E substitution in HIV-1 reverse transcriptase has been selected by tenofovir and results in low-level reduced susceptibility to abacavir, emtricitabine, lamivudine and tenofovir. Viruses that expressed 3 or more thymidine-analogue associated mutations (TAMs) that included either the M41L or L210W RT mutation showed reduced response to tenofovir.

HIV-1 resistance to emtricitabine develops as the result of the M184V mutation in the RT. This HIV-1 mutation was observed *in vitro* and in HIV-1 infected patients in primary prevention trials. A case of tenofovir resistance involving virus expressing the combination of D67N and K70R substitutions has been observed, but it is unclear whether this mutation is naturally transmitted or it emerged during therapy with emtricitabine/tenofovir disoproxil. Emtricitabine-resistant viruses were cross-resistant to lamivudine, but retained sensitivity to other nucleoside reverse transcriptase inhibitors (NRTIs) (zidovudine, stavudine, tenofovir, abacavir, didanosine and zalcitabine), all non-nucleoside reverse transcriptase inhibitors (NNRTIs) and all protease inhibitors (PIs).

In two clinical studies of HIV-1 seronegative subjects [iPrEx Trial, PartnersPrEP Trial], no amino acid substitutions associated with resistance to emtricitabine or tenofovir were detected at the time of seroconversion among 60 subjects in the emtricitabine/tenofovir disoproxil groups and 134 subjects in the placebo groups who became infected with HIV-1 during the trial. However, in some of the 24 subjects who had acute HIV infection at study enrollment, 184V and M184I mutations were detected in 4 subjects (one in the placebo group), and the K65R mutation in one subject.

## 5.2 Pharmacokinetic properties

The absorption characteristics of [HA417 trade name] have been determined after administration of single tablets in healthy volunteers in the fasting state as follows:

| **Pharmacokinetic variable** | **Mean value* (± standard deviation)** | |
|---|---|---|
| | **Emtricitabile** | **Tenofovir** |
| Maximum concentration ($C_{max}$) | 1737 (±425) ng/ml | 311 (±87) ng/ml |
| Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption | 8747 (±1636) ng·h/ml | 1563 (±572) ng·h/ml § |
| Time to attain maximum concentration ($t_{max}$) | 1.45(± 0.59) h | 0.96 (± 0.27) h |

***** Arithmetic mean
§ $AUC_{0-72h}$

Pharmacokinetics of Emtricitabine and Tenofovir disoproxil

| | **Emtricitabine** | **Tenofovir** |
|---|---|---|
| **General** | NA | 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 | 75-93% | NA |
| Oral bioavailability | NA | 25% in fasted patients |
| Food effect | Food does not affect absorption | <table><tr><th></th><th>$AUC_{(0-\infty)}$</th><th>$C_{max}$</th><th>$T_{max}$</th></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> High fat meal increased oral bioavailability |
| Volume of distribution (mean) | After IV admin 1.4L/kg | approximately 800 mL/kg |
| Plasma proteinbinding*in vitro* | < 4% | < 0.7% (serum protein binding |
| Tissue distribution | Widely distributed in body<br>Mean plasma: blood concentration ratio=1.0<br>Mean semen:plasma concentration ratio=4.0 | Well distributed, with highest concentrations in kidney and liver |
| **Metabolism** | oxidation of thiol moiety (approx 9% of dose) and glucuronic acid conjugation (approx 4% of dose) | In vitro studies have determined that neither tenofovir disoproxil nor tenofovir is a substrate for the CYP450 enzymes - |
| Active metabolite(s) | None | Tenofovir |

| | | |
|---|---|---|
| Elimination half life | Approximately 10 h<br>Emtricitabine triphosphate: 39 h in intracellular peripheral blood mononuclear cells | 12 to 18 hours.<br>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) | averaged<br>307 mL/min(4.03 mL/min/kg). | Approximately 210 mL/h/kg (approximately 300 mL/min). |
| % of dose excreted in urine | approximately 86% recovered in urine<br>13% recovered in urine as three metabolites | 70-80% unchanged drug |
| % of dose excreted in faeces | approximately 14% | NA |
| **Pharmacokinetic linearity** | Linear pharmacokinetics (dose range 25 to 200 mg) | Linear pharmacokinetics (dose range 75 to 600 mg) |
| **Drug interactions *(in vitro)*** | | |
| Transporters | NA | Substrate of hOAT 1, hOAT3 and MRP 4 |
| Metabolizing enzymes | No inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4.<br>No inhibition of UGT1A1 | No significant inhibition ofCYP3A4, CYP2D6, CYP2C9, CYP2E1, or CYP1A1/2 |

*NA= Not available

*Special populations*

Age

Pharmacokinetic studies have not been performed with efavirenz, emtricitabine or tenofovirdisoproxilin elderly patients (over 65 years of age).

Gender

The pharmacokinetics of emtricitabine and tenofovir are not clinically significant different in male and female patients. Limited data suggest that females may have higher exposure to efavirenz but they do not appear to be less tolerant of efavirenz.

Ethnicity

No clinically important pharmacokinetic difference due to ethnicity has been identified for emtricitabine. Limited data suggest that Asian and Pacific Island patients may have higher exposure to efavirenz.

Paediatric population

Pharmacokinetic studies have not been performed with the fixed dose combination of efavirenz, emtricitabine and tenofovirdisoproxil in infants and children under 18 years of age (see section 4.2).

Renal impairment

The pharmacokinetics of efavirenz, emtricitabine and tenofovir disoproxil after co-administration of the separate pharmaceutical forms or as fixed dose combination have not been studied in HIV infected patients with renal impairment.

Pharmacokinetic parameters were determined following administration of single doses of the individual preparations of emtricitabine 200 mg or tenofovir disoproxil 245 mg to non-HIV infected patients with varying degrees of renal impairment. The degree of renal impairment was defined according to baseline creatinine clearance (normal renal function when creatinine clearance > 80 mL/min; mild impairment with

creatinine clearance=50 to 79 mL/min; moderate impairment with creatinine clearance=30 to 49 mL/min and severe impairment with creatinine clearance=10 to 29 mL/min).

The mean (%CV) emtricitabine exposure increased from 12 µg·h/mL (25%) in subjects with normal renal function to 20 µg·h/mL (6%), 25 µg·h/mL (23%) and 34 µg·h/mL (6%) in patients with mild, moderate and severe renal impairment, respectively.

The mean (%CV) tenofovir exposure increased from 2,185 ng·h/mL (12%) in patients with normal renal function, to 3,064 ng·h/mL (30%), 6,009 ng·h/mL (42%) and 15,985 ng·h/mL (45%) in patients with mild, moderate and severe renal impairment, respectively.

In patients with end-stage renal disease (ESRD) requiring haemodialysis, between dialysis drug exposures substantially increased over 72 hours to 53 µg·h/mL (19%) of emtricitabine, and over 48 hours to 42,857 ng·h/mL (29%) of tenofovir.

The pharmacokinetics of efavirenz have not been studied in patients with renal impairment. However, less than 1% of an efavirenz dose is excreted unchanged in the urine, so the impact of renal impairment on exposure to efavirenz is likely to be minimal.

[HA417 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 dose interval adjustment of emtricitabine and tenofovir disoproxil that cannot be achieved with the combination tablet (see sections 4.2 and 4.4).

Hepatic impairment

The pharmacokinetics of the fixed dose combination of efavirenz, emtricitabine and tenofovir has not been studied in HIV infected patients with hepatic impairment. [HA417 trade name]should be administered with caution to patients with mild hepatic impairment (see sections 4.3 and 4.4).

[HA417 trade name] must not be used in patients with severe hepatic impairment (see section 4.3) and is not recommended for patients with moderate hepatic impairment. In a single-dose study of efavirenz, half-life was doubled in the single patient with severe hepatic impairment (Child-Pugh-Turcotte Class C), indicating a potential for a much greater degree of accumulation. A multiple-dose study of efavirenz showed no significant effect on efavirenz pharmacokinetics in patients with mild hepatic impairment (Child-Pugh-Turcotte Class A) compared with controls. There were insufficient data to determine whether moderate or severe hepatic impairment (Child-Pugh-Turcotte Class B or C) affects efavirenz pharmacokinetics.

The pharmacokinetics of emtricitabine have not been studied in non-HBV infected patients with varying degrees of hepatic insufficiency. In general, emtricitabine pharmacokinetics in HBV infected patients were similar to those in healthy subjects and in HIV infected patients.
A single 300 mg dose of tenofovir disoproxil was administered to non-HIV infected patients with varying degrees of hepatic impairment defined according to CPT classification. Tenofovir pharmacokinetics were not substantially altered in subjects with hepatic impairment suggesting that no dose adjustment of tenofovir disoproxil is required in these subjects.

## 5.3 Preclinical safety data

Non-clinical data on emtricitabine reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity. Emtricitabine did not show any carcinogenic potential in long-term oral carcinogenicity studies in mice and rats.

Preclinical studies of tenofovir disoproxil conducted in rats, dogs and monkeys revealed target organ effects in 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. The mechanisms of these toxicities are not completely understood.

Conventional reproductive/developmental toxicity studies with emtricitabine and tenofovir disoproxil reveal no special hazard for humans.

Tenofovir disoproxil was positive in two out of three in vitro genotoxicity studies but negative in the in vivo micronucleus assay.

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 concentrations 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. The combination of emtricitabine and tenofovir disoproxil was positive in the in vitro mouse lymphoma assay, with comparable results to those obtained for tenofovir disoproxil alone. The combination of emtricitabine and tenofovir disoproxil was negative in the bacterial reverse mutation assay (Ames assay).

A one month dog study using the combination of emtricitabine and tenofovir disoproxil, found no exacerbation of toxicological effects compared to the separate components.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of Excipients

*Core tablet*

Croscarmellose sodium
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose

*Film coat*

FD&C Blue#2
Hypromellose
Lactose monohydrate
Titanium dioxide
Triacetin

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

24 months in blisters.

36 months in bottles.

## 6.4 Special precautions for storage

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

## 6.5 Nature and contents of container

Cold form Al/Al blister pack consisting of blister foil with heat seal coating on one side and cold form laminate on the other side.
Pack size: 10 tablets per blister card and 3 blister cards per carton (total of 30 tablets).

White opaque HDPE bottle fitted with a white opaque cap and containing a desiccant.
Pack sizes: 28, 30 and 100 tablets.

Blue opaque HDPE bottle with blue opaque polypropylene screw cap and containing a desiccant.
Pack size: 30 tablets.

## 6.6 Special precautions for disposal

No special requirements.

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

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

## 7. SUPPLIER

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## 8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

HA417

## 9. DATE OF PREQUALIFICATION

20 August 2010

## 10. DATE OF REVISION OF THE TEXT

June 2020

**References**

General reference sources for this SmPC include:

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*All weblinks were last accessed on 30 January 2019*

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