WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

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

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

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

1. NAME OF THE MEDICINAL PRODUCT

[HA620 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each tablet contains 153 mg of lactose monohydrate.

3. PHARMACEUTICAL FORM

Film-coated tablets

White to off white, capsule shaped, biconvex (rounded on top and bottom), film coated tablet, debossed (stamped into) with 'I' on one side and '49' on other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Treatment of HIV

[HA620 trade name] is indicated in combination with another antiretroviral medicine for the treatment of human immunodeficiency virus (HIV) infection in adults and adolescents weighing at least 30 kg.

Pre-exposure prophylaxis (PrEP)

[HA620 trade name] may be used for pre-exposure prophylaxis (PrEP) in combination with other measures in adults and adolescents (weighing at least 30 kg) who are at substantial risk of HIV infection.

Post-exposure prophylaxis (PEP)

[HA620 trade name] is indicated, preferably in combination with another antiretroviral medicine, for post-exposure prophylaxis (PEP) in adults and adolescents weighing at least 30 kg who have been exposed to HIV.

For the use of antiretroviral medicines for both treatment and prevention of HIV infection, health care providers should consult the most recent official guidelines, such as those of the World Health Organization (WHO).

Treatment of chronic Hepatitis B infection in adults and adolescents (when tenofovir monotherapy is not available)

[HA620 trade name] is indicated for the treatment of chronic hepatitis B in adults and adolescents with:

- evidence of significant fibrosis or evidence of cirrhosis based on clinical criteria; or
- hepatitis B virus (HBV) DNA > 2000 IU/mL and alanine aminotransferase (ALT) level above the upper limit of normal (ULN), (for adolescents, ALT>ULN at least twice in a 6- to 12-month period) or, if HBV DNA assay is not available, persistently raised ALT levels over 6 to 12 months; or
- presence of co-infections (such as with HIV, hepatitis C or D); a family history of liver cancer or cirrhosis; immune suppression; comorbidities (such as diabetes, liver steatosis); or extrahepatic manifestations of HBV infection (such as glomerulonephritis or vasculitis).

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

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

4.2. Posology and method of administration

Therapy with [HA620 trade name] should be initiated by a health care provider experienced in the management of HIV infection or treatment of chronic hepatitis B infection.

Posology

HIV treatment

The recommended dose of [HA620 trade name] is one tablet, taken once daily together with another antiretroviral.

Daily pre-exposure prophylaxis (PrEP)

The recommended dose of [HA620 trade name] for daily PrEP is 1 tablet once a day. Daily PrEP should start 7 days before a person's potential exposure. When intending to stop daily PrEP, the person should have PrEP for 7 days after the last potential exposure.

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

Adult males who are not taking exogenous estradiol-based hormones can also have event-driven PrEP. For event-driven PrEP, the person should take 2 tablets 2 to 24 hours before potential exposure and then continue with one tablet once a day until two days after the last potential exposure. (see section 4.4)

Post-exposure prophylaxis (PEP)

The recommended dose of [HA620 trade name] for PEP is one tablet once daily for 28 days in combination with another antiretroviral. PEP should start as early as possible after exposure and ideally within 72 hours of exposure.

Chronic hepatitis B treatment (when tenofovir monotherapy is not available)

The recommended dose of [HA620 trade name] for the treatment of chronic hepatitis B in adults and adolescents from 12 years of age is one tablet once daily.

Special populations

Children and adolescents

[HA620 trade name] should not be used in children and adolescents weighing less than 30 kg since appropriate dose adjustment cannot be achieved with product (see section 5.2).

Elderly

[HA620 trade name] should be administered with caution to elderly patients (see section 4.4).

Renal impairment

[HA620 trade name] is not recommended for use in HIV patients with creatinine clearance < 50 mL/minute (see sections 4.4. and 5.2), as [HA620 trade name] is a fixed dose combination formulation, and appropriate dose adjustments are not possible. For these patients, separate formulations of lamivudine and tenofovir should be used.

[HA620 trade name] should not be used for PrEP in HIV uninfected individuals with estimated creatinine clearance below 60 mL/minute as it has not been studied.

[HA620 trade name] is not recommended to treat chronic hepatitis B in patients with renal impairment.

Hepatic impairment

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

Discontinuation of therapy

HIV

Where stopping HIV treatment with one of the components of [HA620 trade name] is indicated or where dose modification is necessary, separate preparations of lamivudine and tenofovir disoproxil should be used. If [HA620 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).

Chronic hepatitis B

Antiviral therapy is lifelong. Discontinuing [HA620 trade name] may be considered exceptionally for:

- people without clinical evidence of cirrhosis
- who can be followed carefully after discontinuation and long term for reactivation
- if there is evidence of HBeAg loss and seroconversion to anti-HBe (for people initially HBeAg-positive) and after completion of at least one additional year of treatment
- in association with persistently normal ALT levels and persistently undetectable HBV DNA levels

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

If treatment with [HA620 trade name] is discontinued in patients with chronic hepatitis B (with or without HIV co-infection), the patient should be closely monitored for evidence of exacerbation of hepatitis (see section 4.4).

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

Retreatment (chronic hepatitis B)

Relapse is common after stopping therapy with [HA620 trade name]. Retreatment is recommended if there are consistent signs of reactivation: HBsAg or HBeAg becomes positive, ALT levels increase, or HBV DNA becomes detectable again.

Missed dose

If a dose of [HA620 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 [HA620 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 [HA620 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 [HA620 trade name].

Method of administration:

It is recommended that [HA620 trade name] be swallowed whole with water. [HA620 trade name] can be taken with food or between meals.

For 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.

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

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 and hepatitis B*). In turn, HBV antibody testing should be offered to all individuals before initiating tenofovir therapy.

Pre-exposure prophylaxis

[HA620 trade name] is not always effective at preventing HIV-1 infection. 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 (there is some evidence that emtricitabine and lamivudine are pharmacologically and clinically equivalent). People who report exposure to HIV before protection from PrEP has been achieved should be considered for post-exposure prophylaxis.

[HA620 trade name] should only be used for pre-exposure prophylaxis as part of a comprehensive prevention strategy that includes other prevention measures, such as safer sex practices.

Individuals should be counselled about safer sex practices that include using condoms consistently and correctly, knowing their HIV status and that of their partner(s), and testing regularly for other sexually transmitted infections that can facilitate HIV transmission (such as syphilis and gonorrhoea).

Risk of resistance with undetected HIV infection

Only an individual who has been confirmed HIV-negative should use [HA620 trade name] for PrEP. Use of [HA620 trade name] alone in an individual with undetected HIV-1 infection can lead to the virus developing resistance to the drug. Individuals with HIV infection must be treated with an additional antiretroviral.

Many HIV tests, such as rapid tests, detect anti-HIV antibodies and may not identify HIV during the acute stage of infection. Prior to initiating [HA620 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 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 status should be then reconfirmed using a reliable test before starting [HA620 trade name] for pre-exposure prophylaxis.

While using [HA620 trade name] for PrEP, HIV screening tests should be repeated at least every 3 months. If symptoms consistent with acute HIV infection develop following a potential exposure event, PrEP should be discontinued until negative infection status is confirmed using a reliable test for diagnosing HIV.

Event-driven PrEP

Event-driven PrEP is solely recommended for cisgender men and transgender and gender-diverse people **assigned male at birth**, who have sexual exposure and are not taking exogenous estradiol-based hormones. Event driven PrEP is most suitable for men who have sex with men (MSM) who have sexual activities that are planned at least 2 hours in advance or can be delayed for at least 2 hours.

Cisgender women and transgender and gender-diverse people assigned female at birth, cisgender men and trans and gender-diverse people assigned male at birth who are taking exogenous estradiol-based hormones, and people using oral PrEP to prevent HIV acquisition from injecting practices may use the daily pre-exposure prophylaxis (PrEP) instead.

Importance of adherence

Uninfected individuals should be counselled to strictly adhere to the recommended [HA620 trade name] dosing schedule. The effectiveness of tenofovir in reducing the risk of acquiring HIV correlates strongly with adherence.

Adherence to post-exposure prophylaxis (PEP) regimen

Individuals should be counselled to adhere to the recommended [HA620 trade name] 28-day dosing schedule for PEP. Adherence to a full 28-day course of antiretroviral drugs for post-exposure prophylaxis is critical to the effectiveness of the intervention.

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 lifestyle. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. 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 infected patients receiving [HA620 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. [HA620 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 [HA620 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 [HA620 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 [HA620 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

[HA620 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 [HA620 trade name].

Children and adolescents

Data on the long-term safety of antiviral therapy for adolescents are still limited. Longer-term studies of bone and kidney health among children are currently not available to determine whether these effects continue to accumulate over time and may result in reduced peak bone mineral density achieved during adolescence or are time-limited in magnitude, as observed for adults . Children and adolescents may experience significant

hepatitis flares after stopping nucleos(t)ide analogue treatment, which sometimes requires retreatment. There are particular concerns about such flares occurring with unplanned and therefore generally unmonitored discontinuation of treatment during adolescence. Although this concern alone should not be a reason to avoid treatment. (see flares after treatment discontinuation below)

Bone effects

Reductions of bone mineral density (BMD) have been observed with tenofovir disoproxil in randomized controlled clinical trials of duration up to 144 weeks in HIV or HBV-infected patients (see also section 4.8). These BMD decreases generally improved after treatment discontinuation. Over 144 weeks, the risk of fractures was not increased and there was no evidence of clinically relevant bone abnormalities. Nonetheless, in view of the bone abnormalities associated with tenofovir disoproxil and the limitations of long-term data on the impact of tenofovir disoproxil on bone health and fracture risk, benefit-risk should be considered carefully for patients with osteoporosis or with a history of bone fractures. In HIV-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, [HA620 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 [HA620 trade name] should be stopped immediately if clinical signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur.

Liver disease

The safety and efficacy of [HA620 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.

Co-infection with HIV and hepatitis viruses

Due to the risk of development of HIV resistance, [HA620 trade name] should be used only as part of an appropriate antiretroviral combination regimen in HIV and **HBV** co-infected patients. Patients with liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities

during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered. However, it should be noted that increases of ALT can be part of HBV clearance during therapy with tenofovir (see below, Flares on treatment').

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

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-ups 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

Direct-acting antiviral therapy is generally considered safe and effective for people with HIV and HCV but it is important to consider the relevant interactions (see section 4.5).

Co-administration of other medicinal products

As a fixed combination, [HA620 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, [HA620 trade name] should not be administered concomitantly with other cytidine analogues, such as emtricitabine. [HA620 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 congenital lactase deficiency, galactosaemia or glucose-galactose intolerance must not be given this medicine unless strictly necessary. The small amount of lactose in each dose is unlikely to cause symptoms of lactose intolerance in other patients.

Patients who are allergic to cow's milk proteins must not be given this medicine unless strictly necessary.

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

No drug interaction studies have been conducted using [HA620 trade name]. Drug interaction studies have been conducted in adults 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.

As a fixed combination, [HA620 trade name] should not be administered concomitantly with other medicinal products containing either of the same active components, lamivudine or tenofovir.

Interactions relevant to lamivudine

Metabolic interactions with lamivudine are less likely because of its limited metabolism and plasma protein binding and almost complete renal clearance.

Lamivudine metabolism does not involve CYP3A and interactions with medicines metabolised by this system (e.g. protease inhibitors) are unlikely.

Medicines which are mainly eliminated by renal secretion via the organic cationic transport system, e.g. trimethoprim, may interact with 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. The concomitant use of [HA620 trade name] with high doses of sulfamethoxazole/trimethoprim (e.g. for treating *Pneumocystis jirovecii* pneumonitis) is not recommended.

Medicines (e.g. ranitidine, cimetidine), which are eliminated only in part by this mechanism, were shown not to interact with lamivudine.

Due to similarities with lamivudine, [HA620 trade name] should not be administered concomitantly with other cytidine analogues, such as emtricitabine. Moreover, [HA620 trade name] should not be taken with any other medicinal products containing lamivudine.

In vitro lamivudine inhibits the intracellular phosphorylation of cladribine, raising the possibility of a loss of cladribine's efficacy if the two are used concomitantly. Some clinical findings also support a possible interaction between lamivudine and cladribine. Therefore, the concomitant use of [HA620 trade name] with cladribine is not recommended.

Co-administration 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, avoid chronic co-administration of [HA620 trade name] with medicinal products containing sorbitol or other osmotic acting polyalcohols or monosaccharide alcohols (e.g., xylitol, mannitol, lactitol, maltitol). Consider more frequent monitoring of HIV-1 viral load when chronic co-administration cannot be avoided.

The co-administration of sulfadiazine and cisplatin with lamivudine has a potential for renal toxicity and would require monitoring of renal function.

The co-administration of flucytosine with lamivudine has potential for haematological toxicity which requires monitoring of haematological parameters and dose reduction should be considered.

Interactions relevant to tenofovir

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.

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.

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

[HA620 trade name] should not be administered with any other medicines containing:

- tenofovir disoproxil
- tenofovir alafenamide
- adefovir dipivoxil
- didanosine

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.

Some key interactions between the components of [HA620 trade name] and co-administered medicinal products are listed in the following table

Medicines by therapeutic area	**Interaction Changes shown as geometric mean**	**Recommendations on co-administration**
ANTI-INFECTIVES		
Antiretrovirals		
Nucleoside reverse transcriptase inhibitors (NRTI)		

Medicines by therapeutic area	**Interaction Changes shown as geometric mean**	**Recommendations on co-administration**
Emtricitabine / lamivudine		[HA620 trade name] should not be co-administered, due to the similarity between emtricitabine and lamivudine, and consequently expected additive toxicity and no benefit in efficacy.
Didanosine / tenofovir disoproxil	Didanosine AUC ↑ 40-60%	The risk of didanosine-related adverse effects (e.g., pancreatitis, lactic acidosis) appears to be increased, and CD4-cells may decrease significantly on co-administration. Also didanosine at 250 mg co-administered with tenofovir disoproxil within several different antiretroviral combination regimens has been associated with a high rate of virological failure. Co-administration of [HA620 trade name] and didanosine is not recommended.
Adefovir dipivoxil/ tenofovir disoproxil	AUC: ↔ C_{max}: ↔	Tenofovir disoproxil should not be administered concurrently with adefovir dipivoxil.
Entecavir/ tenofovir disoproxil	AUC: ↔ C_{max}: ↔	No clinically significant pharmacokinetic interactions when tenofovir disoproxil was co-administered with entecavir.
Protease inhibitors (PIs)		
Atazanavir+ritonavir/ Tenofovir disoproxil	Tenofovir: AUC: ↑ 37%; C_{max}: ↑ 34%; C_{min}: ↑ 29% Atazanavir: AUC: ↓ 25%; C_{max}: ↓ 28%; C_{min}: ↓ 26%	The increased exposure of tenofovir could potentiate tenofovir-associated adverse events, including renal disorders. Renal function should be closely monitored.
Darunavir+ritonavir/ Tenofovir disoproxil	Darunavir: No significant effect on darunavir/ritonavir PK parameters. Tenofovir: AUC: ↑ 22%; C_{min}: ↑ 37%	The increased exposure of tenofovir could potentiate tenofovir-associated adverse events, including renal disorders. Renal function should be closely monitored.
Lopinavir+ritonavir/ Tenofovir disoproxil	Lopinavir/ritonavir: No significant effect on lopinavir/ritonavir PK parameters. Tenofovir: AUC: ↑ 32%; Cmax: ↔; Cmin: ↑ 51%	The increased exposure of tenofovir could potentiate tenofovir-associated adverse events, including renal disorders. Renal function should be closely monitored.
Antivirals against hepatitis C		
Daclatasvir/tenofovir disoproxil	Daclatasvir ↔ AUC : 1.10 (1.01, 1.21) C_{max}: 1.06 (0.98, 1.15) Cmin: 1.15 (1.02, 1.30) Tenofovir ↔ AUC: 1.10 (1.05, 1.15) C_{max}: 0.95 (0.89, 1.02) C_{min}: 1.17 (1.10, 1.24)	No dose adjustment is necessary.

Medicines by therapeutic area	Interaction Changes shown as geometric mean	Recommendations on co-administration
Sofosbuvir/tenofovir disoproxil	Tenofovir ↑ C_{max} 1.25 (1.08, 1.45) ↔ AUC 0.98 (0.91, 1.05) ↔ C_{min} 0.99 (0.91, 1.07) Sofosbuvir ↓ C_{max} 0.81 (0.60, 1.10) ↔ AUC 0.94 (0.76, 1.16) C_{min} (NA) GS-331007 (predominant inactive metabolite of sofosbuvir) ↓ C_{max} 0.77 (0.70, 0.84) ↔ AUC 0.84 (0.76, 0.92) C_{min} (NA)	No dose adjustment of sofosbuvir or [HA620 trade name] is required when sofosbuvir and [HA620 trade name] are used concomitantly.
Ledipasvir/sofosbuvir +dolutegravir + Tenofovir disoproxil (+emtricitabine)	Sofosbuvir : AUC: ↔; C_{max}: ↔ GS-331007: AUC: ↔; C_{max}: ↔; C_{min}: ↔ Ledipasvir: AUC: ↔; C_{max}: ↔ $C_{min:}$ ↔ Dolutegravir: AUC: ↔; C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔; C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 65; C_{max}: ↑ 61% C_{min}: ↑ 115%	No dose adjustment is recommended. Monitor for tenofovir-associated adverse reactions in patients receiving ledipasvir/sofosbuvir concomitantly with [HA620 trade name]. Renal function should be closely monitored.
Antimycobacterials		
Antifungals		
Fluconazole Itraconazole Ketoconazole Posaconazole Voriconazole	Tenofovir disoproxil: ↑	Itraconazole or ketoconazole co-administration may increase tenofovir exposure. Monitoring of tenofovir-associated adverse reactions, including frequent renal monitoring, is recommended. Based on theoretical considerations, no interaction with dolutegravir or lamivudine is expected.
Flucytosine/ lamivudine/ tenofovir disoproxil		Potential haematological toxicity. Monitor haematological parameters and consider dose reduction if required.
OTHER MEDICINES		
Analgesics		

Medicines by therapeutic area	Interaction Changes shown as geometric mean	Recommendations on co-administration
Aspirin (analgesic) /ibuprofen + Tenofovir disoproxil		No pharmacokinetic interaction expected. However, co-administration could potentially result in increased risk of nephrotoxicity. Alternatives to NSAIDs should be considered in patients at risk for renal dysfunction. If tenofovir disoproxil is co-administered with an NSAID, renal function should be monitored adequately.
Antiarrhythmics		
Amiodarone/tenofovir disoproxil Quinidine/tenofovir disoproxil		Co-administration may increase tenofovir exposure. Monitoring of tenofovir-associated adverse reactions, including frequent renal monitoring, is recommended.
Cancer Therapies		
Cisplatin		Tenofovir disoproxil and lamivudine: potential renal toxicity. Monitor renal function.
Oxaliplatin	Co-administration of dolutegravir decrease oxaliplatin efficacy. Tenofovir Disoproxil: ↑	Dolutegravir: co-administration may decrease the efficacy of oxaliplatin. When possible, use raltegravir. Tenofovir disoproxil: potential renal toxicity. Monitor renal function. Lamivudine: weak interaction, no dose adjustment required.
Dacarbazine	Co-administration may increase tenofovir and dacarbazine exposure.	No a priori dosage adjustment is recommended but renal function and haematological parameters should be monitored.

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 breast-feeding

Pregnancy

[HA620 trade name] may be used in 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). Data on exposure in pregnant women do not indicate any effect on the fetus associated with tenofovir disoproxil or lamivudine.

Breast-feeding

Lamivudine and tenofovir disoproxil are excreted into the breast milk of lactating mothers. Tenofovir is excreted in human milk at very low levels and exposure of infants through breast milk is considered negligible.

If [HA620 trade name] is being given *for HIV infection or prophylaxis*, current recommendations on HIV and breast-feeding (e.g. those from the WHO) should be consulted before advising patients on whether to breast-feed. 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.

Adverse reactions considered related to tenofovir disoproxil and lamivudine are listed below by body system or organ. Frequencies are defined as follows: very common (at least 1 in 10), common (1 in 100 to 1 in 10) uncommon (1 in 1000 to 1 in 100), rare (1 in 10 000 to 1 in 1000), very rare (less than 1 in 10 000) or not known (frequency cannot be estimated from available data).

Blood and lymphatic systems disorders	
Uncommon	neutropenia, anaemia (occasionally severe), thrombocytopenia
Very rare	pure red cell aplasia
Metabolism and nutrition disorders:	
Very common	hypophosphataemia
Rare	lactic acidosis
Uncommon	hypokalaemia
Nervous system disorders	
Very common	headache, dizziness
Very rare	Peripheral neuropathy (paraesthesia)
Gastrointestinal disorders	
Very common	nausea, diarrhoea, vomiting
Common	flatulence, abdominal pain, abdominal distension, pancreatitis
Rare	elevated serum amylases
Hepatobiliary disorders	
Common	raised alanine aminotransferase (ALT) and aspartate aminotransferase (AST)
Rare	Hepatitis, hepatic steatosis
Skin and subcutaneous tissue disorders	
Very common	rash
Common	alopecia
Rare	angioedema

Musculoskeletal and connective tissue disorders

Common	arthralgia, muscle disorders, decreased bone mineral density[3]
Uncommon	myalgia, rhabdomyolysis[1], muscular weakness[1]
Rare	osteomalacia (manifested as bone pain and infrequently contributing to fractures)[1, 2] myopathy[1]

Renal and urinary disorders

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

General disorders

Very common	asthenia
Common	fatigue, malaise, fever

Investigations

Common	raised creatine phosphokinase (CPK)

[1]This adverse reaction may occur as a consequence of proximal renal tubulopathy. It is not considered to be causally associated with tenofovir disoproxil in the absence of this condition.
[2]This adverse reaction was identified through post-marketing surveillance.
[3] The frequency of this adverse reaction was estimated based on safety data derived from different clinical studies with TDF in HBV infected patients.

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 Partners PrEP 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) 9

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 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).

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

Children

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 of suspected adverse reactions

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

4.9. Overdose

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

For lamivudine, if overdose occurs, the patient should be monitored, and standard supportive treatment applied as required. Since lamivudine is dialysable, continuous haemodialysis could be used in the treatment of overdose, although this has not been studied.

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.

[‡] 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.

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.

Data pertaining to HIV

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

HIV treatment

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**Error! Bookmark not defined.** 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**Error! Bookmark not defined.**/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.

Data pertaining to chronic hepatitis B

Pharmacodynamic effects

Antiviral activity in cell culture (tenofovir dixoproxil)

The *in vitro* antiviral activity of tenofovir against HBV was assessed in the HepG2 2.2.15 cell line. The EC_{50} values for tenofovir were in the range of 0.14 to 1.5 µ mol/l, with CC_{50} (50% cytotoxicity concentration) values > 100 µ mol/L.

Resistance:

No HBV mutations associated with tenofovir disoproxil resistance have been identified (see Clinical efficacy and safety). In cell based assays, HBV strains expressing the rtV173L, rtL180M, and rtM204I/V mutations associated with resistance to lamivudine and telbivudine showed a susceptibility to tenofovir ranging from 0.7- to 3.4-fold that of wild-type virus. HBV strains expressing the rtL180M, rtT184G, rtS202G/I, rtM204V and rtM250V mutations associated with resistance to entecavir showed a susceptibility to tenofovir ranging from 0.6- to 6.9-fold that of wild-type virus. HBV strains expressing the adefovir-associated resistance mutations rtA181V and rtN236T showed a susceptibility to tenofovir ranging from 2.9- to 10-fold that of wild-type virus. Viruses containing the rtA181T mutation remained susceptible to tenofovir with EC_{50} values 1.5-fold that of wild-type virus.

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

Clinical efficacy and safety

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

Experience in patients with compensated liver disease at 48 weeks (studies GS-US-174-0102 and GS-US-174-0103)

Results through 48 weeks from two randomised, phase 3 double-blind studies comparing tenofovir disoproxil to adefovir dipivoxil in adult patients with compensated liver disease are presented in Table 3 below. Study GS-US-174-0103 was conducted in 266 (randomised and treated) HBeAg positive patients while study GS-US-174-0102 was conducted in 375 (randomised and treated) patients negative for HBeAg and positive for HBeAb.

In both of these studies tenofovir disoproxil was significantly superior to adefovir dipivoxil for the primary efficacy endpoint of complete response (defined as HBV DNA levels < 400 copies/mL and Knodell necroinflammatory score improvement of at least 2 points without worsening in Knodell fibrosis). Treatment with tenofovir disoproxil 245 mg was also associated with significantly greater proportions of patients with HBV DNA < 400 copies/mL, when compared to adefovir dipivoxil 10 mg treatment. Both treatments produced similar results with regard to histological response (defined as Knodell necroinflammatory score improvement of at least 2 points without worsening in Knodell fibrosis) at week 48.

In study GS-US-174-0103 a significantly greater proportion of patients in the tenofovir disoproxil group than in the adefovir dipivoxil group had normalised ALT and achieved HBsAg loss at week 48.

Clinical experience (lamivudine)

Experience in patients with HBeAg positive CHB and compensated liver disease

In controlled studies, 1 year of lamivudine therapy significantly suppressed HBV DNA replication [34-57% of patients were below the assay detection limits (Abbott Genostics solution hybridization assay, LLOD < 1.6 pg/ml)}, normalised ALT level (40-72% of patients), induced HBeAg seroconversion (HBeAg loss and HBeAb detection with HBV DNA loss [by conventional assay], 16-18% of patients), improved histology (38-52% of patients had a ≥ 2 point decrease in the Knodell Histologic Activity Index [HAI]) and reduced progression of fibrosis (in 3-17% of patients) and progression to cirrhosis.

Continued lamivudine treatment for an additional 2 years in patients who had failed to achieve HBeAg seroconversion in the initial 1 year controlled studies resulted in further improvement in bridging fibrosis. In patients with YMDD mutant HBV, 41/82 (50%) patients had improvement in liver inflammation and 40/56 (71%) patients without YMDD mutant HBV had improvement. Improvement in bridging fibrosis occurred in 19/30 (63%) patients without YMDD mutant and 22/44 (50%) patients with the mutant. Five percent (3/56) of patients without the YMDD mutant and 13% (11/82) of patients with YMDD mutant showed worsening in liver inflammation compared to pre-treatment. Progression to cirrhosis occurred in 4/68 (6%) patients with the YMDD mutant, whereas no patients without the mutant progressed to cirrhosis.

5.2. Pharmacokinetic properties

The absorption characteristics of [HA620 trade name] have been determined after administration of one lamivudine/tenofovir disoproxil fumarate 300 mg/300 mg tablets in healthy volunteers in the fed state as follows:

Pharmacokinetic variable	**Mean value* (± standard deviation)**	
	Tenofovir	**Lamivudine**
Maximum concentration (C_{max}) ng/mL	404 ± 109	2776 ± 786

Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption) ng.h/mL	3213 ± 757	13389 ± 3182
Time to attain maximum concentration (T_{max}) hours	1.22 ±0.54	1.60 ± 0.55

Pharmacokinetics of tenofovir disoproxil and lamivudine

	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: 10 h 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

[HA620 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.

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.

The pharmacokinetics of tenofovir in paediatric patients with renal impairment have not been studied. No data are available to make dose recommendations. (See section 4.2 and 4.4)

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. The pharmacokinetics of lamivudine were not altered by diminishing hepatic function. Safety and efficacy of lamivudine have not been established in the presence of decompensated liver disease.

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

Microcrystalline cellulose

Partially pregelatinized maize starch

Sodium starch glycolate

Film coat: Hypromellose

Macrogol/PEG

Polysorbate

Titanium dioxide

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

6.2. Incompatibilities

Not applicable

6.3. Shelf life

24 months

6.4. Special precautions for storage

Do not store above 30ºC

6.5. Nature and contents of container

[HA620 trade name] are packed in round, white opaque plastic (HDPE) bottles, with round white polyethylene child resistant cap with heat induction containing 30 or 100 tablets

6.6. Special precautions for disposal and other handling

No special requirements.

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

7. SUPPLIER

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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

HA620

9. DATE OF PREQUALIFICATION

09 July 2015

10. DATE OF REVISION OF THE TEXT

November 2024

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