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

[HA792 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with potential clinical effect

Each film-coated tablet also contains 62.2 mg lactose monohydrate.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet

Light blue, capsule-shaped, film coated tablets. They are biconvex (rounded on top and bottom) with a flat edge. The tablets have 'D17' debossed (stamped into) one side and are plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prevention of HIV infection

Treatment of HIV

[HA792 trade name] is indicated in combination with another antiretroviral medicine for the treatment of HIV infection in adults and adolescents weighing at least 30 kg.

HIV pre-exposure prophylaxis (PrEP)

[HA792 trade name] is indicated 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.

HIV post-exposure prophylaxis (PEP)

[HA792 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.

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

Treatment of hepatitis B

[HA792 trade name] can be used in the treatment of chronic hepatitis B if tenofovir disoproxil fumarate alone is not available. It is used for chronic hepatitis B treatment in adults and adolescents from 12 years of age with any of the following features:

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

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

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

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

4.2 Posology and method of administration

Treatment with [HA792 trade name] should be initiated by a health care provider experienced in the management of HIV infection or hepatitis B.

Posology

HIV treatment

The recommended dose of [HA792 trade name] for the treatment of HIV infection in patients weighing 30 kg or more is 1 tablet once a day.

Daily pre-exposure prophylaxis (PrEP) of HIV

The recommended dose of [HA792 trade name] for daily PrEP is 1 tablet once a day. Daily PrEP should start 7 days before a person's potential exposure. When intending to stop daily PrEP, the person should have PrEP for 7 days after the last potential exposure.

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

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

Post-exposure prophylaxis (PEP) of HIV

The recommended dose of [HA792 trade name] for PEP is one tablet once daily for 28 days. PEP should start as early as possible after exposure and ideally within 72 hours of exposure.

Hepatitis B treatment

The recommended dose of [HA792 trade name] for the treatment of chronic hepatitis B in patients from 12 years of age is 1 tablet once a day.

Duration of hepatitis B treatment

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

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

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

Paediatric population

[HA792 trade name] should not be used in children and adolescents weighing less than 30 kg.

Elderly

There is no need for dose adjustment of [HA792 trade name] in the elderly (see section 5.2).

Renal impairment

Emtricitabine and tenofovir are both eliminated by renal excretion, and exposure to both compounds increases in patients with renal dysfunction (see sections 4.4 and 5.2).

[HA792 trade name] should only be used for HIV/hepatitis B treatment or PrEP in adults with creatinine clearance (CrCl) < 80 mL/min if the potential benefits are considered to outweigh the potential risks (see Table 1). For PEP, health care providers should consult appropriate official guidelines.

Table 1: Dosing recommendations for HIV/hepatitis B treatment and HIV PrEP in adults with renal impairment

	Treatment of HIV/hepatitis B	**HIV Pre-exposure prophylaxis**
Mild renal impairment (CrCl 50-80 mL/min)	Limited data from clinical studies support once daily dosing (see section 4.4).	Limited data from clinical studies support once daily dosing in HIV-uninfected individuals with CrCl 60-80 mL/min. Use is not recommended in HIV-uninfected individuals with CrCl < 60 mL/min as it has not been studied in this population (see sections 4.4 and 5.2).
Moderate renal impairment (CrCl 30-49 mL/min)	Administration 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).	Not recommended for use in this population
Severe renal impairment (CrCl < 30 mL/min) and haemodialysis patients	Not recommended because appropriate dose reductions cannot be achieved with the combination tablet.	Not recommended for use in this population

Children with renal impairment

[HA792 trade name] is not recommended for HIV/hepatitis B treatment or HIV PrEP in individuals under the age of 18 years with renal impairment (see section 4.4). For HIV PEP, health care providers should consult appropriate official guidelines.

Hepatic impairment

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

Missed dose

If a dose of [HA792 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 [HA792 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 should simply resume the usual dosing schedule.

If the individual vomits within 1 hour of taking [HA792 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 [HA792 trade name].

Method of administration

[HA792 trade name] is taken orally with food or between meals.

The tablets may be crushed and added to a small amount (approximately 100 mL) of water, orange juice or grape juice, 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.

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

4.4 Special warnings and precautions for use

Patients with HIV harbouring mutations

[HA792 trade name] should be avoided in antiretroviral-experienced patients with HIV harbouring the K65R mutation (see section 5.1).

Overall strategy for preventing HIV infection with pre-exposure prophylaxis (PrEP)

[HA792 trade name] is not always effective at preventing HIV infection. Pharmacological studies suggest that the number of doses to be taken before daily 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.

[HA792 trade name] should only be used for pre-exposure prophylaxis as part of a comprehensive prevention strategy which involves other preventive 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 take [HA792 trade name] for PrEP (see section 4.3). HIV resistance substitutions may emerge in individuals with undetected HIV infection who are taking only emtricitabine and tenofovir disoproxil, because these do not constitute a complete treatment regimen for HIV.

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 emtricitabine and tenofovir disoproxil for pre-exposure prophylaxis, seronegative individuals should also be evaluated for current or recent signs or symptoms consistent with acute viral infections (e.g. fever, fatigue, myalgia and skin rash) and asked about potential exposure (e.g. from unprotected sex or condom breakage during sex with an HIV-infected partner) that may have occurred within the last month.

If clinical symptoms consistent with acute viral infection are present and recent HIV-exposure (within the last month) is suspected, PrEP should be delayed for at least one month. The person's HIV status should be confirmed before starting [HA792 trade name] for pre-exposure prophylaxis.

Individuals should be re-confirmed as HIV-negative at frequent intervals (e.g. at least every 3 months) using a combined antigen/antibody test while taking [HA792 trade name] for pre-exposure prophylaxis.

Importance of adherence

Individuals should be counselled to adhere strictly to the recommended [HA792 trade name] dosing schedule. The effectiveness of [HA792 trade name] in reducing the risk of acquiring HIV is strongly correlated with adherence, as demonstrated by measurable drug levels in clinical trials.

Adherence to HIV post-exposure prophylaxis (PEP) regimen

Individuals should be counselled to adhere to the recommended [HA792 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.

Hepatitis B or C virus co-infection in patients with HIV

HIV-infected patients with chronic hepatitis B or C treated with antiretroviral therapy for HIV are at an increased risk for severe and potentially fatal hepatic adverse reactions. Health care providers should refer to current treatment guidelines for the optimal management of HIV infection in patients co-infected with the hepatitis B virus (HBV) or the hepatitis C virus (HCV).

The safety and efficacy of emtricitabine and tenofovir disoproxil for HIV pre-exposure prophylaxis in patients with HBV or HCV infection has not been established.

Tenofovir disoproxil is used for the treatment of HBV and emtricitabine has shown activity against HBV in pharmacodynamic studies. Discontinuation of [HA792 trade name] in HBV-infected patients may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue [HA792 trade name] 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 in patients with HIV

The pharmacokinetics of tenofovir has been studied in patients with hepatic impairment and no dose adjustment is required. The pharmacokinetics of emtricitabine has not been studied in patients with hepatic impairment. Based on the minimal hepatic metabolism and the renal route of elimination of emtricitabine, it is unlikely that a dose adjustment would be required for [HA792 trade name] in patients with hepatic impairment (see also sections 4.2 and 5.2).

HIV-infected 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.

Renal effects in adults

Emtricitabine and tenofovir are primarily excreted by the kidneys by 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 (see section 4.8).

Renal monitoring

Prior to initiating [HA792 trade name] for the treatment of HIV/hepatitis B infection or for use in HIV pre-exposure prophylaxis, baseline renal function may be assessed.

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

In individuals at risk for renal disease, more frequent monitoring of renal function is required (see section on co-administration of other medicinal products below).

Renal management in HIV-infected 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 [HA792 trade name], renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations (see section 4.8, proximal tubulopathy). Consideration should be given to interrupting treatment with [HA792 trade name] in patients with creatinine clearance decreased to < 50 mL/min or decreases in serum phosphate to < 1.0 mg/dL (0.32 mmol/L). Interrupting treatment with [HA792 trade name] should also be considered in case of progressive decline of renal function when no other cause has been identified.

Renal safety with emtricitabine and tenofovir disoproxil has only been studied to a very limited degree in HIV-infected patients with impaired renal function (creatinine clearance < 80 mL/min). Dose interval adjustments are recommended for HIV-infected 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 [HA792 trade name] 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 [HA792 trade name] at a prolonged dosing interval.

The use of [HA792 trade name] is not recommended in patients with severe renal impairment (creatinine clearance < 30 mL/min) and in patients who require haemodialysis since appropriate dose reductions cannot be achieved with the combination tablet (see sections 4.2 and 5.2).

Renal management in pre-exposure prophylaxis

Combination treatment with emtricitabine and tenofovir disoproxil has not been studied in HIV uninfected individuals with creatinine clearance < 60 mL/min and is therefore not recommended for use in this population. If the serum phosphate level is < 1.5 mg/dL (0.48 mmol/L) or creatinine clearance is decreased to < 60 mL/min in any individual receiving [HA792 trade name] for pre-exposure prophylaxis, 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 be given to interrupting use of [HA792 trade name] in individuals with creatinine clearance decreased to < 60 mL/min or decreases in serum phosphate to < 1.0 mg/dL (0.32 mmol/L). Interrupting use of [HA792 trade name] should also be considered in case of progressive decline of renal function when no other cause has been identified.

Bone effects in adults

Bone abnormalities such as osteomalacia which can manifest as persistent or worsening bone pain and which can infrequently contribute to fractures may be associated with tenofovir disoproxil-induced proximal renal tubulopathy (see section 4.8). Tenofovir disoproxil may also cause a reduction in bone mineral density (BMD).

If bone abnormalities are suspected or detected, then appropriate consultation should be obtained.

Treatment of HIV infection

Reductions of bone mineral density (BMD) have been observed with tenofovir disoproxil in randomized controlled clinical trials lasting up to 144 weeks in HIV or HBV-infected patients. These BMD decreases generally improved after treatment discontinuation.

In other studies (prospective and cross-sectional), the most pronounced decreases in BMD were seen in patients treated with tenofovir disoproxil as part of a regimen containing a boosted protease inhibitor. Overall, in view of the bone abnormalities associated with tenofovir disoproxil and the limitations of long-term data on the impact of tenofovir disoproxil on bone health and fracture risk, alternative treatment regimens should be considered for patients with osteoporosis or with a history of bone fractures.

Pre-exposure prophylaxis

In clinical studies of HIV-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 the hip, spine and femoral neck and trochanter in men who received daily emtricitabine and tenofovir disoproxil prophylaxis (n = 247) vs. placebo (n = 251).

Renal and bone effects in the paediatric population

There are uncertainties associated with the long-term renal and bone effects of tenofovir disoproxil during the treatment of HIV infection in the paediatric population and the long-term renal and bone effects of emtricitabine and tenofovir disoproxil when used for pre-exposure prophylaxis in uninfected adolescents (see section 5.1). Moreover, the reversibility of renal toxicity after cessation of tenofovir disoproxil for the treatment of HIV or after cessation of [HA792 trade name] for pre-exposure prophylaxis cannot be fully ascertained.

A multidisciplinary approach is recommended to weigh the benefit/risk balance of the use of [HA792 trade name] for the treatment of HIV infection or for pre-exposure prophylaxis, decide the

appropriate monitoring during treatment (including decision for treatment withdrawal) and consider the need for supplementation on a case-by-case basis.

When using [HA792 trade name] for pre-exposure prophylaxis, individuals should be reassessed at each visit to ascertain whether they remain at high risk of HIV infection. The risk of HIV infection should be balanced against the potential for renal and bone effects with long-term use of [HA792 trade name].

Renal effects

Renal adverse reactions consistent with proximal renal tubulopathy have been reported in HIV-infected paediatric patients aged 2 to < 12 years in clinical study GS-US-104-0352 (see sections 4.8 and 5.1).

Renal monitoring

Renal function (creatinine clearance and serum phosphate) should be evaluated prior to initiating [HA792 trade name] for treatment of HIV or for pre-exposure prophylaxis and should be monitored during use as in adults (see above).

Renal management

If serum phosphate is confirmed to be < 3.0 mg/dL (0.96 mmol/L) in any paediatric patient receiving [HA792 trade name], renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations (see section 4.8, proximal tubulopathy). If renal abnormalities are suspected or detected, consultation with a nephrologist should be obtained to consider interruption of [HA792 trade name] use. Interrupting use of [HA792 trade name] should also be considered in case of progressive decline of renal function when no other cause has been identified.

Co-administration and risk of renal toxicity

The same recommendations apply as in adults (see Co-administration of other medicinal products below).

Renal impairment

The use of [HA792 trade name] is not recommended in individuals under the age of 18 years with renal impairment (see section 4.2). [HA792 trade name] should not be initiated in paediatric patients with renal impairment and should be discontinued in paediatric patients who develop renal impairment during [HA792 trade name] use.

Bone effects

Use of tenofovir disoproxil may cause a reduction in BMD. The effects of tenofovir disoproxil-associated changes in BMD on long-term bone health and future fracture risk are uncertain (see section 5.1).

If bone abnormalities are detected or suspected during the use of [HA792 trade name] in any paediatric patient, consultation with an endocrinologist and/or nephrologist should be obtained.

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.

Mitochondrial dysfunction following exposure in utero

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 reconstitution 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. cytomegalovirus 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.

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 by health care providers experienced in the treatment of patients with HIV-associated diseases.

Osteonecrosis

Osteonecrosis has been reported particularly in patients with advanced HIV-disease and/or long-term exposure to CART. Its aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Co-administration of other medicinal products

Use of emtricitabine and tenofovir disoproxil should be avoided with concurrent or recent use of a nephrotoxic medicinal product (see section 4.5). If concomitant use with nephrotoxic agents is unavoidable, renal function should be monitored weekly.

Cases of acute renal failure after initiation of high dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs) have been reported in HIV-infected patients treated with tenofovir disoproxil and with risk factors for renal dysfunction. If emtricitabine and tenofovir disoproxil is co-administered with an NSAID, renal function should be monitored adequately.

A higher risk of renal impairment has been reported in HIV-infected patients receiving tenofovir disoproxil in combination with a ritonavir or cobicistat boosted protease inhibitor. Close monitoring of renal function is required in these patients (see section 4.5). In HIV-infected patients with renal risk factors, the co-administration of tenofovir disoproxil with a boosted protease inhibitor should be carefully evaluated.

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.

Use of tenofovir disoproxil with: ledipasvir and sofosbuvir; sofosbuvir and velpatasvir; or sofosbuvir, velpatasvir and voxilaprevir

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.

Co-administration of tenofovir disoproxil and didanosine

Co-administration of tenofovir disoproxil and didanosine is not recommended (see section 4.5).

Triple nucleoside therapy

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

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

[HA792 trade name] contains a small amount of lactose 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.

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 [HA792 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 when each medicinal product was 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

[HA792 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 other cytidine analogues, such as lamivudine (see section 4.4 and below).

Didanosine

Co-administration of [HA792 trade name] and didanosine is not recommended (see section 4.4 and Table 2).

Renally eliminated medicinal products

Since emtricitabine and tenofovir are primarily eliminated by the kidneys, co-administration of [HA792 trade name] with medicinal products that reduce renal function or compete for active tubular secretion (e.g. cidofovir) may increase serum concentrations of emtricitabine, tenofovir and/or the co-administered medicinal products.

Use of [HA792 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 emtricitabine and tenofovir disoproxil and other medicinal products are listed in Table 2 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 emtricitabine and/or tenofovir disoproxil with and other medicinal products

Medicinal products taken with tenofovir disoproxil and/or emtricitabine	**Mean % change in AUC, C_{max} and C_{min} with 90% confidence intervals if available**	**Recommendation concerning co-administration with [HA792 trade name]**
ANTI-INFECTIVES		
Antiretrovirals		
Protease inhibitors		
Atazanavir/Ritonavir/Tenofovir disoproxil (300 mg q.d./100 mg q.d./245 mg q.d.)	Atazanavir: AUC: ↓ 25% (↓ 42 to ↓ 3) C_{max}: ↓ 28% (↓ 50 to ↑ 5) C_{min}: ↓ 26% (↓ 46 to ↑ 10) 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).
Atazanavir/Ritonavir/Emtricitabine	Interaction not studied.	
Darunavir/Ritonavir/Tenofovir disoproxil (300 mg q.d./100 mg q.d./245 mg q.d.)	Darunavir: AUC: ↔ C_{min}: ↔ 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).
Darunavir/Ritonavir/Emtricitabine	Interaction not studied.	
Lopinavir/Ritonavir/Tenofovir disoproxil (400 mg b.i.d./100 mg b.i.d/245 mg q.d.)	Lopinavir/Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 32% (↑ 25 to ↑ 38) C_{max}: ↔ C_{min}: ↑ 51% (↑ 37 to ↑ 66)	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/Emtricitabine	Interaction not studied.	
NRTIs		
Didanosine/Tenofovir disoproxil	Co-administration of tenofovir disoproxil and didanosine results in a 40 - 60% increase in systemic exposure to didanosine.	Co-administration of [HA792 trade name] and didanosine is not recommended (see section 4.4).

Medicinal products taken with tenofovir disoproxil and/or emtricitabine	**Mean % change in AUC, C_{max} and C_{min} with 90% confidence intervals if available**	**Recommendation concerning co-administration with [HA792 trade name]**
		Increased systemic exposure to didanosine may increase didanosine-related adverse reactions. Rarely, 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. A decreased dosage of 250 mg didanosine co-administered with tenofovir disoproxil therapy has been associated with reports of high rates of virological failure within several tested combinations for the treatment of HIV infection.
Didanosine/Emtricitabine	Interaction not studied.	
Lamivudine/Tenofovir disoproxil	Lamivudine: AUC: ↓ 3% (↓ 8% to ↑ 15) C_{max}: ↓ 24% (↓ 44 to ↓ 12) C_{min}: NC Tenofovir: AUC: ↓ 4% (↓ 15 to ↑ 8) C_{max}: ↑ 102% (↓ 96 to ↑ 108) C_{min}: NC	Lamivudine and [HA792 trade name] should not be administered concomitantly (see section 4.4).
Efavirenz/Tenofovir disoproxil	Efavirenz: AUC: ↓ 4% (↓ 7 to ↓ 1) C_{max}: ↓ 4% (↓ 9 to ↑ 2) C_{min}: NC Tenofovir: AUC: ↓ 1% (↓ 8 to ↑ 6) C_{max}: ↑ 7% (↓ 6 to ↑ 22) C_{min}: NC	No dose adjustment of efavirenz is required.
Hepatitis B virus (HBV) antiviral agents		
Adefovir dipivoxil/Tenofovir disoproxil	Adefovir dipivoxil: AUC: ↓ 11% (↓ 14 to ↓ 7) C_{max}: ↓ 7% (↓ 13 to ↓ 0) C_{min}: NC Tenofovir: AUC: ↓ 2% (↓ 5 to ↑ 0) C_{max}: ↓ 1% (↓ 7 to ↑ 6) C_{min}: NC	Adefovir dipivoxil and [HA792 trade name] should not be administered concomitantly (see section 4.4).

Medicinal products taken with tenofovir disoproxil and/or emtricitabine	**Mean % change in AUC, C_{max} and C_{min} with 90% confidence intervals if available**	**Recommendation concerning co-administration with [HA792 trade name]**
Hepatitis C virus (HCV) antiviral agents		
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Atazanavir/Ritonavir (300 mg q.d./100 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)[1]	Ledipasvir: AUC: ↑ 96% (↑ 74 to ↑ 121) C_{max}: ↑ 68% (↑ 54 to ↑ 84) C_{min}: ↑ 118% (↑ 91 to ↑ 150) Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 42% (↑ 34 to ↑ 49) Atazanavir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 63% (↑ 45 to ↑ 84) Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 45% (↑ 27 to ↑ 64) Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↑ 47% (↑ 37 to ↑ 58) C_{min}: ↑ 47% (↑ 38 to ↑ 57)	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. The combination should be used with caution with frequent renal monitoring, if other alternatives are not available (see section 4.4).
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Darunavir/Ritonavir (800 mg q.d./100 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)[1]	Ledipasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Sofosbuvir: AUC: ↓ 27% (↓ 35 to ↓ 18) C_{max}: ↓ 37% (↓ 48 to ↓ 25) GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Darunavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Ritonavir:	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, ledipasvir/sofosbuvir and darunavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with ledipasvir/sofosbuvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring, if other alternatives are not available (see section 4.4).

Medicinal products taken with tenofovir disoproxil and/or emtricitabine	**Mean % change in AUC, C_{max} and C_{min} with 90% confidence intervals if available**	**Recommendation concerning co-administration with [HA792 trade name]**
	AUC: ↔ C_{max}: ↔ C_{min}: ↑ 48% (↑ 34 to ↑ 63) Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 50% (↑ 42 to ↑ 59) C_{max}: ↑ 64% (↑ 54 to ↑ 74) C_{min}: ↑ 59% (↑ 49 to ↑ 70)	
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Efavirenz/Emtricitabine/Tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)	Ledipasvir: AUC: ↓ 34% (↓ 41 to ↓ 25) C_{max}: ↓ 34% (↓ 41 to ↑ 25) C_{min}: ↓ 34% (↓ 43 to ↑ 24) Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 98% (↑ 77 to ↑ 123) C_{max}: ↑ 79% (↑ 56 to ↑ 104) C_{min}: ↑ 163% (↑ 137 to ↑ 197)	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4).
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Emtricitabine/Rilpivirine/ Tenofovir disoproxil (200 mg/25 mg/245 mg q.d.)	Ledipasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4).

Medicinal products taken with tenofovir disoproxil and/or emtricitabine	**Mean % change in AUC, C_{max} and C_{min} with 90% confidence intervals if available**	**Recommendation concerning co-administration with [HA792 trade name]**
	Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Rilpivirine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 40% (↑ 31 to ↑ 50) C_{max}: ↔ C_{min}: ↑ 91% (↑ 74 to ↑ 110)	
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Dolutegravir (50 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2] AUC: ↔ C_{max}: ↔ C_{min}: ↔ Ledipasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Dolutegravir AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 65% (↑ 59 to ↑ 71) C_{max}: ↑ 61% (↑ 51 to ↑ 72) C_{min}: ↑ 115% (↑ 105 to ↑ 126)	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).
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Atazanavir/Ritonavir (300 mg q.d./100 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 42% (↑ 37 to ↑ 49) Velpatasvir: AUC: ↑ 142% (↑ 123 to ↑ 164) C_{max}: ↑ 55% (↑ 41 to ↑ 71) C_{min}: ↑ 301% (↑ 257 to ↑ 350)	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.

Medicinal products taken with tenofovir disoproxil and/or emtricitabine	**Mean % change in AUC, C_{max} and C_{min} with 90% confidence intervals if available**	**Recommendation concerning co-administration with [HA792 trade name]**
	Atazanavir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 39% (↑ 20 to ↑ 61) Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 29% (↑ 15 to ↑ 44) Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↑ 55% (↑ 43 to ↑ 68) C_{min}: ↑ 39% (↑ 31 to ↑ 48)	ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring (see section 4.4).
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Darunavir/Ritonavir (800 mg q.d./100 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↓ 28% (↓ 34 to ↓ 20) C_{max}: ↓ 38% (↓ 46 to ↓ 29) GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Velpatasvir: AUC: ↔ C_{max}: ↓ 24% (↓ 35 to ↓ 11) C_{min}: ↔ Darunavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 39% (↑ 33 to ↑ 44) C_{max}: ↑ 55% (↑ 45 to ↑ 66) 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. 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	Sofosbuvir: AUC: ↓ 29% (↓ 36 to ↓ 22) C_{max}: ↓ 41% (↓ 51 to ↓ 29)	Increased plasma concentrations of tenofovir resulting from co-

Medicinal products taken with tenofovir disoproxil and/or emtricitabine	**Mean % change in AUC, C_{max} and C_{min} with 90% confidence intervals if available**	**Recommendation concerning co-administration with [HA792 trade name]**
(800 mg/200 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)	GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Velpatasvir: AUC: ↔ C_{max}: ↓ 30% (↓ 41 to ↓ 17) C_{min}: ↑ 63% (↑ 43 to ↑ 85) Lopinavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↑ 42% (↑ 27 to ↑ 57) C_{min}: ↔	administration of tenofovir disoproxil, sofosbuvir/velpatasvir and lopinavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with sofosbuvir/velpatasvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring (see section 4.4).
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Raltegravir (400 mg b.i.d) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Velpatasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Raltegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↓ 21% (↓ 58 to ↑ 48) Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 40% (↑ 34 to ↑ 45)	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 taken with tenofovir disoproxil and/or emtricitabine	**Mean % change in AUC, C_{max} and C_{min} with 90% confidence intervals if available**	**Recommendation concerning co-administration with [HA792 trade name]**
	C_{max}: ↑ 46% (↑ 39 to ↑ 54) C_{min}: ↑ 70% (↑ 61 to ↑ 79)	
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Efavirenz/Emtricitabine/Tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ C_{max}: ↑ 38% (↑ 14 to ↑ 67) GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Velpatasvir: AUC: ↓ 53% (↓ 61 to ↓ 43) C_{max}: ↓ 47% (↓ 57 to ↓ 36) C_{min}: ↓ 57% (↓ 64 to ↓ 48) Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 81% (↑ 68 to ↑ 94) C_{max}: ↑ 77% (↑ 53 to ↑ 104) 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: AUC: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Velpatasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Rilpivirine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir:	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 taken with tenofovir disoproxil and/or emtricitabine	**Mean % change in AUC, C_{max} and C_{min} with 90% confidence intervals if available**	**Recommendation concerning co-administration with [HA792 trade name]**
	AUC: ↑ 40% (↑ 34 to ↑ 46) C_{max}: ↑ 44% (↑ 33 to ↑ 55) 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/Tenofovir disoproxil (200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ C_{max}: ↓ 30% C_{min}: N/A GS-331007[2]: AUC: ↔ C_{max}:↔ C_{min}: N/A Velpatasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Voxilaprevir: AUC: ↑ 143% C_{max}:↑ 72% C_{min}: ↑ 300% Darunavir: AUC: ↔ C_{max}: ↔ C_{min}: ↓ 34% Ritonavir: AUC: ↑ 45% C_{max}: ↑ 60% C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 39% C_{max}: ↑ 48% 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. The combination should be used with caution with frequent renal monitoring (see section 4.4).
Sofosbuvir (400 mg q.d.) + Efavirenz/Emtricitabine/Tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ C_{max}: ↓ 19% (↓ 40 to ↑ 10) GS-331007[2]: AUC: ↔ C_{max}: ↓ 23% (↓ 30 to ↑ 16) Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔	No dose adjustment is required.

Medicinal products taken with tenofovir disoproxil and/or emtricitabine	**Mean % change in AUC, C_{max} and C_{min} with 90% confidence intervals if available**	**Recommendation concerning co-administration with [HA792 trade name]**
	Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↑ 25% (↑ 8 to ↑ 45) C_{min}: ↔	
Ribavirin/Tenofovir disoproxil	Ribavirin: AUC: ↑ 26% (↑ 20 to ↑ 32) C_{max}: ↓ 5% (↓ 11 to ↑ 1) C_{min}: NC	No dose adjustment of ribavirin is required.
Herpes virus antiviral agents		
Famciclovir/Emtricitabine	Famciclovir: AUC: ↓ 9% (↓ 16 to ↓ 1) C_{max}: ↓ 7% (↓ 22 to ↑ 11) C_{min}: NC Emtricitabine: AUC: ↓ 7% (↓ 13 to ↓ 1) C_{max}: ↓ 11% (↓ 20 to ↑ 1) C_{min}: NC	No dose adjustment of famciclovir is required.
Antimycobacterials		
Rifampicin/Tenofovir disoproxil	Tenofovir: AUC: ↓ 12% (↓ 16 to ↓ 8) C_{max}: ↓ 16% (↓ 22 to ↓ 10) C_{min}: ↓ 15% (↓ 12 to ↓ 9)	No dose adjustment is required.
ORAL CONTRACEPTIVES		
Norgestimate/Ethinyl oestradiol/Tenofovir disoproxil	Norgestimate: AUC: ↓ 4% (↓ 32 to ↑ 34) C_{max}: ↓ 5% (↓ 27 to ↑ 24) C_{min}: NC Ethinyl oestradiol: AUC: ↓ 4% (↓ 9 to ↑ 0) C_{max}: ↓ 6% (↓ 13 to ↑ 0) C_{min}: ↓ 2% (↓ 9 to ↑ 6)	No dose adjustment of norgestimate/ethinyl oestradiol is required.
IMMUNOSUPPRESSANTS		
Tacrolimus/Tenofovir disoproxil/Emtricitabine	Tacrolimus: AUC: ↑ 4% (↓ 3 to ↑ 11) C_{max}: ↑ 3% (↓ 3 to ↑ 9) C_{min}: NC Emtricitabine: AUC: ↓ 5% (↓ 9 to ↓ 1) C_{max}: ↓ 11% (↓ 17 to ↓ 5) C_{min}: NC Tenofovir: AUC: ↑ 6% (↓ 1 to ↑ 13) C_{max}: ↑13% (↑ 1 to ↑ 27)	No dose adjustment of tacrolimus is required.

Medicinal products taken with tenofovir disoproxil and/or emtricitabine	Mean % change in AUC, C_{max} and C_{min} with 90% confidence intervals if available	Recommendation concerning co-administration with [HA792 trade name]
	C_{min}: NC	
NARCOTIC ANALGESICS		
Methadone/Tenofovir disoproxil	Methadone: AUC: ↑ 5% (↓ 2 to ↑ 13) C_{max}: ↑ 5% (↓ 3 to ↑ 14) C_{min}: NC	No dose adjustment of methadone is required.

NC = not calculated
N/A = not applicable
[1] Data generated from simultaneous dosing with ledipasvir/sofosbuvir. Staggered administration (12 hours apart) provided similar results.
[2] The predominant circulating metabolite of sofosbuvir.
[3] Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

Food effect

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

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

A large amount of data on pregnant women (more than 1,000 pregnancy outcomes) indicate no malformations or fetal/neonatal toxicity associated with emtricitabine and tenofovir disoproxil.

Animal studies on emtricitabine and tenofovir disoproxil do not indicate reproductive toxicity (see section 5.3). Therefore, the use of [HA792 trade name] may be considered during pregnancy, if necessary.

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

No human data on the effect of [HA792 trade name] are available. Animal studies do not indicate harmful effects of emtricitabine or 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

Summary of the safety profile

In a trial using emtricitabine and tenofovir disoproxil to treat 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 previous experience with these agents when each was administered with other antiretroviral agents.

No new adverse reactions to emtricitabine and tenofovir disoproxil were identified from two randomised placebo-controlled studies (iPrEx, Partners PrEP) in which 2,830 HIV-uninfected adults received emtricitabine and tenofovir disoproxil once daily for pre-exposure prophylaxis. Patients were followed for a median of 71 weeks and 87 weeks, respectively. The most frequent adverse reaction reported in the emtricitabine and tenofovir disoproxil group in the iPrEx study was headache (1%).

Tabulated summary of adverse reactions

The adverse reactions considered at least possibly related to treatment with the components of [HA792 trade name] from clinical trial and post-marketing experience are listed below by body system organ class and 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).

Table 3: Tabulated summary of adverse reactions associated with the individual components of [HA792 trade name] based on clinical study and post-marketing experience

Frequency	Emtricitabine	Tenofovir disoproxil
Blood and lymphatic system disorders		
Common	neutropenia	
Uncommon	anaemia[1]	
Immune system disorders		
Common	allergic reaction	
Metabolism and nutrition disorders		
Very common		hypophosphataemia[2]
Common	hyperglycaemia, hypertriglyceridaemia	
Uncommon		hypokalaemia[2]
Rare		lactic acidosis
Psychiatric disorders		
Common	insomnia, abnormal dreams	
Nervous system disorders		
Very common	headache	dizziness
Common	dizziness	headache
Gastrointestinal disorders		
Very common	diarrhoea, nausea	diarrhoea, vomiting, nausea
Common	elevated amylase including elevated pancreatic amylase, elevated serum lipase, vomiting, abdominal pain, dyspepsia	abdominal pain, abdominal distension, flatulence
Uncommon		pancreatitis

Frequency	Emtricitabine	Tenofovir disoproxil
Hepatobiliary disorders		
Common	elevated serum aspartate aminotransferase (AST) and/or elevated serum alanine aminotransferase (ALT), hyperbilirubinaemia	increased transaminases
Rare		hepatic steatosis, hepatitis
Skin and subcutaneous tissue disorders		
Very common		rash
Common	vesiculobullous rash, pustular rash, maculopapular rash, rash, pruritus, urticaria, skin discoloration (increased pigmentation)[2]	
Uncommon	angioedema[3]	
Rare		angioedema
Musculoskeletal and connective tissue disorders		
Very common	elevated creatine kinase	
Common		decreased bone mineral density
Uncommon		rhabdomyolysis,[2] muscular weakness[2]
Rare		osteomalacia (manifested as bone pain and infrequently contributing to fractures),[2,3] myopathy[2]
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)[3], nephrogenic diabetes insipidus
General disorders and administration site conditions		
Very common		asthenia
Common	pain, asthenia	

[1] Anaemia was common and skin discoloration (increased pigmentation) was very common when emtricitabine was administered to paediatric patients.
[2] 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.
[3] This adverse reaction was identified through post-marketing surveillance but not observed in randomised controlled clinical studies in adults or paediatric HIV clinical studies for emtricitabine or in randomised controlled clinical studies or the tenofovir disoproxil expanded access program for tenofovir disoproxil. The frequency category was estimated

from a statistical calculation based on the total number of patients exposed to emtricitabine in randomised controlled clinical studies (n = 1,563) or tenofovir disoproxil in randomised controlled clinical studies and the expanded access program (n = 7,319).

Description of selected adverse reactions

Renal impairment

As [HA792 trade name] 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 HIV-infected 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).

Lactic acidosis

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

Metabolic parameters

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

Immune reconstitution syndrome

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (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

Assessment of adverse reactions related to emtricitabine is based on experience in three paediatric studies (n = 169) where treatment-naïve (n = 123) and treatment-experienced (n = 46) paediatric HIV-infected patients aged 4 months to 18 years were treated with emtricitabine in combination with other antiretroviral agents. In addition to the adverse reactions reported in adults, anaemia (9.5%) and skin discoloration (31.8%) occurred more frequently in clinical trials in paediatric patients than in adults (see section 4.8, Tabulated summary of adverse reactions).

Assessment of adverse reactions related to tenofovir disoproxil is based on two randomised trials (studies GS-US 104-0321 and GS-US-104-0352) in 184 HIV-infected paediatric patients (aged 2 to < 18 years) who received treatment with tenofovir disoproxil (n = 93) or placebo/active comparator (n = 91) in combination with other antiretroviral agents for 48 weeks (see section 5.1). 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 (see section 4.8 Tabulated summary of adverse reactions and 5.1).

Reductions in bone mineral density (BMD) have been reported in paediatric patients. In HIV-infected adolescents (aged 12 to < 18 years), the BMD Z-scores observed in subjects who received tenofovir disoproxil were lower than those observed in subjects who received placebo. In HIV-infected children (aged 2 to 15 years), the BMD Z-scores observed in subjects who switched to tenofovir disoproxil were lower than those observed in subjects who remained on their stavudine- or zidovudine-containing regimen (see sections 4.4 and 5.1).

In study GS-US-104-0352, 89 HIV-infected paediatric patients with a median age of 7 years (range 2 to 15 years) were exposed to tenofovir disoproxil for a median of 331 weeks. Eight of the 89 patients (9.0%) discontinued study drug due to renal adverse events. Five subjects (5.6%) had laboratory findings clinically consistent with proximal renal tubulopathy, 4 of whom discontinued tenofovir disoproxil therapy. Seven patients had estimated glomerular filtration rate (GFR) values between 70 and 90 mL/min/1.73 m^2. Among them, 3 patients experienced a clinically meaningful decline in estimated GFR during therapy which improved after discontinuation of tenofovir disoproxil.

Other special populations

Individuals with renal impairment

Since tenofovir disoproxil can cause renal toxicity, close monitoring of renal function is recommended in any adults with renal impairment receiving [HA792 trade name] (see sections 4.2, 4.4 and 5.2). The use of [HA792 trade name] is not recommended in individuals under the age of 18 years with renal impairment (see sections 4.2 and 4.4).

HIV/HBV or HCV co-infected patients

The adverse reaction profile of emtricitabine and tenofovir disoproxil in a limited number of HIV-infected patients in study GS-01-934 who were co-infected with HBV (n=13) or HCV (n=26) was similar to that observed in patients infected with HIV without co-infection. However, as would be expected in this population, elevations in AST and ALT occurred more frequently than in the general HIV-infected population.

Exacerbations of hepatitis after discontinuation of treatment

In HBV infected patients, clinical and laboratory evidence of hepatitis have occurred after discontinuation of treatment (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

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.

Both active substances also inhibit HBV polymerase and are active against the hepatitis B virus.

Antiviral activity in vitro

Synergistic antiviral activity was observed with the combination of emtricitabine and tenofovir in vitro. Additive to synergistic effects were observed in combination studies with protease inhibitors, and with nucleoside and non-nucleoside analogue inhibitors of HIV reverse transcriptase.

Resistance

In vitro

Resistance has been seen in vitro and in some HIV-1-infected patients due to the development of the M184V/I mutation with emtricitabine or the K65R mutation with tenofovir. Emtricitabine-resistant viruses with the M184V/I mutation were cross-resistant to lamivudine but retained sensitivity to didanosine, stavudine, tenofovir and zidovudine. The K65R mutation can also be selected by abacavir or didanosine and results in reduced susceptibility to these agents plus lamivudine, emtricitabine and tenofovir. Tenofovir disoproxil should be avoided in patients with HIV-1 harbouring the K65R mutation. 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. HIV-1 expressing three or more thymidine analogue associated mutations (TAMs) that included either the M41L or L210W reverse transcriptase mutation showed reduced susceptibility to tenofovir disoproxil.

In vivo - treatment of HIV

In an open-label randomised clinical study (GS-01-934) in antiretroviral-naïve patients, genotyping was performed on plasma HIV-1 isolates from all patients with confirmed HIV RNA > 400 copies/mL at weeks 48, 96 or 144 or at the time of early study drug discontinuation. As of week 144:

- The M184V/I mutation developed in 2/19 (10.5%) isolates analysed from patients in the emtricitabine/tenofovir disoproxil/efavirenz group and in 10/29 (34.5%) isolates analysed from the lamivudine/zidovudine/efavirenz group (p-value < 0.05, Fisher's Exact test comparing the emtricitabine+tenofovir disoproxil group to the lamivudine/zidovudine group among all patients).
- No virus analysed contained the K65R or K70E mutation.
- Genotypic resistance to efavirenz, predominantly the K103N mutation, developed in virus from 13/19 (68%) patients in the emtricitabine/tenofovir disoproxil/efavirenz group and in virus from 21/29 (72%) patients in the comparative group.

In vivo - pre-exposure prophylaxis

Plasma samples from 2 clinical studies of HIV-1 uninfected subjects, iPrEx and Partners PrEP, were analysed for 4 HIV-1 variants expressing amino acid substitutions (i.e. K65R, K70E, M184V and M184I) that potentially confer resistance to tenofovir or emtricitabine.

In the iPrEx clinical study, no HIV-1 variants expressing K65R, K70E, M184V, or M184I were detected at the time of seroconversion among subjects who became infected with HIV-1 after enrolment in the study. In 3 of 10 subjects who had acute HIV infection at study enrolment, M184I and M184V mutations were detected in the HIV of 2 of 2 subjects in the tenofovir/emtricitabine group and 1 of 8 subjects in the placebo group.

In the Partners PrEP clinical study, no HIV-1 variants expressing K65R, K70E, M184V, or M184I were detected at the time of seroconversion among subjects who became infected with HIV-1 during the study. In 2 of 14 subjects who had acute HIV infection at study enrolment, the K65R mutation was detected in the HIV of 1 of 5 subjects in the tenofovir disoproxil 245 mg group and the M184V mutation (associated with resistance to emtricitabine) was detected in the HIV of 1 of 3 subjects in the emtricitabine/tenofovir disoproxil group.

Clinical results

HIV therapy

When tenofovir and emtricitabine were combined with efavirenz in treatment-naïve patients with HIV-1, 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.

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 $\log_{10}$ reduction or 4 to 5 $\log_{10}$ reduction, respectively) (see section 4.4).

Daily HIV pre-exposure prophylaxis

The iPrEx trial was a randomized, double-blind, placebo-controlled multinational study evaluating tenofovir and emtricitabine in 2,499 HIV-seronegative men or transgender women who have sex with men and with evidence of high-risk behaviour for HIV infection. Evidence of high-risk behaviour included any one of the following reported to have occurred up to six months prior to study screening: no condom use during anal intercourse with an HIV-1 positive partner or a partner of unknown HIV status; anal intercourse with more than 3 sex partners; exchange of money, gifts, shelter, or drugs for anal sex; sex with male partner and diagnosis of sexually transmitted infection; no consistent use of condoms with sex partner known to be HIV-1 positive.

All subjects received monthly HIV-1 testing, risk-reduction counselling, condoms, and management of sexually transmitted infections. Of the 2,499 enrolled subjects, 1,251 received a combination of emtricitabine and tenofovir and 1,248 received placebo. The mean age of subjects was 27 years; 5% were Asian, 9% Black, 18% White, and 72% Hispanic/Latino.

Subjects were followed for 4,237 person-years. The primary outcome measure was the incidence of documented HIV seroconversion. At the end of treatment, emergent HIV-1 seroconversion was observed in 131 subjects, of which 48 occurred in the tenofovir and emtricitabine group and 83 occurred in the placebo group, indicating a 42% (95% CI: 18–60%) reduction in risk. Risk reduction was found to be higher (53%; 95% CI: 34–72%) among subjects who reported previous unprotected anal intercourse (URAI) at screening (732 and 753 subjects reported URAI within the last 12 weeks at screening in the tenofovir and emtricitabine group and placebo group, respectively). In a post-hoc case control study of plasma and intracellular drug levels in about 10% of study subjects, risk reduction appeared to be greatest in subjects with detectable intracellular tenofovir diphosphate concentrations. Efficacy was therefore strongly correlated with adherence.

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 in this study was also strongly correlated with adherence.

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

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

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

HIV post-exposure prophylaxis

A systematic review completed in 2018 assessed the tolerability of HIV PEP and completion of different antiretroviral drug regimens. The systematic review identified 16 studies reporting the outcomes of HIV PEP regimens using tenofovir disoproxil fumarate/lamivudine (or emtricitabine) backbones. All studies involved adults, and no additional evidence was retrieved for PEP regimens for children or adolescents. Overall, the highest completion rates for HIV PEP were reported for tenofovir disoproxil fumarate/lamivudine (or emtricitabine) in combination with darunavir/ritonavir (93%, 95% CI 89–97%) or dolutegravir (90%, 95% CI 84–96%). These regimens were also associated with the lowest rates of discontinuation or substitutions because of adverse events (1%, 95% CI 0–2% for darunavir/ritonavir; 1%, 95% CI 1–4% for dolutegravir).

Treatment of hepatitis B

In adults with hepatitis B monoinfection, a systematic review and meta-analysis was undertaken comprising five randomized trials with 633 participants (TDF + FTC = 313, TDF = 320) to assess the effectiveness of dual therapy with TDF + FTC versus TDF.

TDF + FTC did not differ significantly from TDF for the primary outcomes of undetectable HBV DNA (TDF + FTC versus TDF: 80% versus 73%, OR 1.55, 95% CI 0.87–2.76), ALT normalization (TDF + FTC versus TDF: 72% versus 67%, OR 1.30, 95% CI 0.91–1.84), HBsAg loss (2.6% versus 2.0%, OR 1.28, 95% CI 0.24–6.74), HBeAg loss (TDF + FTC versus TDF: 11% versus 14%, OR 0.77, 95% CI 0.41–1.45) and HBeAg seroconversion (TDF + FTC versus TDF: 6.2% versus 9.8%, 0.64, 95% CI 0.26–1.58).

The TDF + FTC and TDF groups also did not differ significantly for safety outcomes, including any adverse events (TDF + FTC versus TDF: 78% versus 81%, OR 0.84, 95% CI 0.38–1.82), grade 3 or 4 adverse events (TDF + FTC versus TDF: 16% versus 13%, OR 1.24, 95% CI 0.48–3.22) or serious adverse events (TDF + FTC versus TDF: 15% versus 11%, OR 1.36, 95% CI 0.48–3.83).

In one double-blind trial with long-term follow-up, people with hepatitis B were randomized to receive TDF or TDF + FTC for 168 weeks, with an option of switching to open-label FTC + TDF if HBV DNA was >69 IU/mL at week 24. At week 168, long-term viral suppression was maintained for 84% of those receiving TDF + FTC and 82% receiving TDF. No resistance to TDF was observed through 168 weeks of treatment.

5.2 Pharmacokinetic properties

The absorption characteristics of [HA792 trade name] have been determined after administration of tablets of [HA792 trade name] in healthy volunteers under fasting conditions as follows:

Pharmacokinetic variable	**Arithmetic mean value ± standard deviation**	
	Emtricitabine	**Tenofovir**
Maximum concentration (C_{max}) ng/mL	13159 ± 2551	335 ± 77
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption ng.h/mL	2575 ± 524	2906 ± 770
Time to attain maximum concentration (t_{max}) h	1.72 ± 0.75	1.21 ± 0.64

Table 4: Pharmacokinetics of emtricitabine and tenofovir disoproxil

	Emtricitabine	**Tenofovir disoproxil**
General	Emtricitabine is rapidly and extensively absorbed following oral administration, with peak plasma concentrations occurring at 1 to 2 hours post-dose. Metabolism is limited and it is excreted mainly by the kidneys.	Tenofovir disoproxil is a water-soluble ester prodrug that is rapidly absorbed and converted to tenofovir which is converted intracellularly to the active component, tenofovir diphosphate. Tenofovir is primarily excreted by the kidneys by both filtration and an active tubular transport system.
Absorption		
Absolute bioavailability	75-93%	NA
Oral bioavailability	NA	25% in fasted patients
Food effect	Food does not affect absorption	$AUC_{(0-\infty)}$: 35%↑; C_{max}: 15%↑; T_{max}: 45 mins ↑
Volume of distribution (mean)	After IV admin 1.4L/kg	Approximately 800 mL/kg
Plasma protein binding *in vitro*	< 4%	< 0.7% (serum protein binding)
Tissue distribution	Widely distributed in body Mean plasma to blood concentration ratio =1.0 Mean semen to plasma concentration ratio=4.0	Well distributed, with highest concentrations in kidney and liver
Metabolism	Limited metabolism. Biotransformation includes 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	12 to 18 hours. Tenofovir diphosphate: 10 hours in intracellular

	Emtricitabine	**Tenofovir disoproxil**
	Emtricitabine triphosphate: 39 h in intracellular peripheral blood mononuclear cells	activated resting peripheral blood mononuclear cells and 50 hours in resting peripheral blood mononuclear cells.
Mean systemic clearance (Cl/F)	Averaged 307 mL/min (4.03 mL/min/kg).	Approximately 230 mL/h/kg (approximately 300 mL/min).
% of dose excreted in urine	Approximately 86% recovered in urine (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	hOAT 1, hOAT3 and MRP 4
Metabolizing enzymes	No inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. No inhibition of uridine-5'-diphosphoglucuronyl transferase	No significant inhibition of CYP3A4, CYP2D6, CYP2C9, CYP2E1, or CYP1A1/2

*NA= Not available

Elderly

Pharmacokinetic studies have not been performed with emtricitabine or tenofovir (administered as tenofovir disoproxil) in the elderly (over 65 years of age).

Gender

Emtricitabine and tenofovir pharmacokinetics are similar in male and female patients.

Ethnicity

No clinically important pharmacokinetic difference due to ethnicity has been identified for emtricitabine. The pharmacokinetics of tenofovir (administered as tenofovir disoproxil) have not been specifically studied in different ethnic groups.

Paediatric population

Pharmacokinetic studies have not been performed with emtricitabine/tenofovir disoproxil in children and adolescents (under 18 years of age). Steady-state pharmacokinetics of tenofovir were evaluated in 8 HIV-1-infected adolescent patients (aged 12 to < 18 years) with body weight ≥ 35 kg and in 23 HIV-1-infected children aged 2 to < 12 years. Tenofovir exposure achieved in these paediatric patients receiving oral daily doses of tenofovir disoproxil 245 mg or 6.5 mg/kg body weight tenofovir disoproxil up to a maximum dose of 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 in children under 2 years. In general, the pharmacokinetics of emtricitabine in infants, children and adolescents (aged 4 months up to 18 years) are similar to those seen in adults.

The pharmacokinetics of emtricitabine and tenofovir (administered as tenofovir disoproxil) are expected to be similar in HIV-1-infected and uninfected adolescents based on the similar exposures of emtricitabine and tenofovir in HIV-1-infected adolescents and adults, and the similar exposures of emtricitabine and tenofovir in HIV-1-infected and uninfected adults.

Renal impairment

Limited pharmacokinetic data are available for emtricitabine and tenofovir after co-administration of separate preparations or as emtricitabine/tenofovir disoproxil in patients with renal impairment. Pharmacokinetic parameters were mainly determined following administration of single doses of emtricitabine 200 mg or tenofovir disoproxil 245 mg to non-HIV-infected subjects with varying degrees of renal impairment. The degree of renal impairment was defined according to baseline creatinine clearance (CrCl) (normal renal function when CrCl > 80 mL/min; mild impairment with CrCl = 50-79 mL/min; moderate impairment with CrCl = 30-49 mL/min and severe impairment with CrCl = 10-29 mL/min).

The mean (%CV) emtricitabine drug exposure increased from 12 (25%) μg·h/mL in subjects with normal renal function, to 20 (6%) μg·h/mL, 25 (23%) μg·h/mL and 34 (6%) μg·h/mL, in subjects with mild, moderate and severe renal impairment, respectively. The mean (%CV) tenofovir drug exposure increased from 2,185 (12%) ng·h/mL in subjects with normal renal function, to 3,064 (30%) ng·h/mL, 6,009 (42%) ng·h/mL and 15,985 (45%) ng·h/mL, in subjects with mild, moderate and severe renal impairment, respectively.

The increased dose interval for emtricitabine/tenofovir disoproxil in HIV-1-infected patients with moderate renal impairment is expected to result in higher peak plasma concentrations and lower C_{min} levels as compared to patients with normal renal function. In subjects with end-stage renal disease (ESRD) requiring haemodialysis, between dialysis drug exposures substantially increased over 72 hours to 53 (19%) μg·h/mL of emtricitabine, and over 48 hours to 42,857 (29%) ng·h/mL of tenofovir.

A small clinical study was conducted to evaluate the safety, antiviral activity and pharmacokinetics of tenofovir disoproxil in combination with emtricitabine in HIV-infected patients with renal impairment. A subgroup of patients with baseline creatinine clearance between 50 and 60 mL/min, receiving once daily dosing, had a 2-4-fold increase in tenofovir exposure and worsening renal function.

The pharmacokinetics of emtricitabine and tenofovir (administered as tenofovir disoproxil) in paediatric patients with renal impairment have not been studied. No data are available to make dose recommendations (see sections 4.2 and 4.4).

Hepatic impairment

The pharmacokinetics of emtricitabine/tenofovir disoproxil have not been studied in subjects with hepatic impairment.

The pharmacokinetics of emtricitabine have not been studied in non-HBV infected subjects with varying degrees of hepatic insufficiency. In general, emtricitabine pharmacokinetics in HBV infected subjects were similar to those in healthy subjects and in HIV-infected patients.

A single 245 mg dose of tenofovir disoproxil was administered to non-HIV-infected subjects with varying degrees of hepatic impairment defined according to Child-Pugh-Turcotte (CPT) classification. Tenofovir pharmacokinetics were not substantially altered in subjects with hepatic impairment suggesting that no dose adjustment is required in these subjects. The mean (%CV) tenofovir C_{max} and $AUC_{0-\infty}$ values were 223 (34.8%) ng/mL and 2,050 (50.8%) ng·h/mL, respectively, in normal subjects compared with 289 (46.0%) ng/mL and 2,310 (43.5%) ng·h/mL in subjects with moderate hepatic impairment, and 305 (24.8%) ng/mL and 2,740 (44.0%) ng·h/mL in subjects with severe hepatic impairment.

5.3 Preclinical safety data

Emtricitabine

Non-clinical data on emtricitabine reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development.

Tenofovir disoproxil

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

Genotoxicity studies revealed positive results in the in vitro mouse lymphoma assay, equivocal results in one of the strains used in the Ames test, and weakly positive results in an unscheduled DNA synthesis (UDS) test in primary rat hepatocytes. However, it was negative in an in vivo mouse bone marrow micronucleus assay.

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

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

Combination of emtricitabine and tenofovir disoproxil

Genotoxicity and repeated dose toxicity studies of one month or less with the combination of these two components found no exacerbation of toxicological effects compared to studies with the separate components.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet: lactose monohydrate
croscarmellose sodium
pregelatinized starch
microcrystalline cellulose
magnesium stearate

Film coat: hypromellose
lactose monohydrate
triacetin
titanium dioxide
FD&C blue #2 /indigo carmine aluminium lake

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 30°C. Store in the original container.

6.5 Nature and contents of container

Round, opaque white plastic (HDPE) bottle containing 30 tablets. It also contains a sachet of desiccant (drying material). The bottle has an aluminium/plastic foil seal and a white plastic (polypropylene) screw cap.

6.6 Special precautions for disposal and other handling

No special requirements

7. SUPPLIER

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