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/pqweb/sites/default/files/documents/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[HA500 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:
Efavirenz 600 mg
Emtricitabine 200 mg
Tenofovir disoproxil fumarate 300 mg

Excipients with known effect

Each tablet contains soya lecithin

For a full list of excipients see 6.1

3. PHARMACEUTICAL FORM

Pink coloured capsule shaped, biconvex film coated tablet with “V” debossed on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[HA500 trade name] is a fixed-dose combination of efavirenz, emtricitabine and tenofovir disoproxil. It is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and adolescents weighing at least 35 kg.
Treatment regimens should follow most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

4.2 Posology and method of administration

[HA500 trade name] is a fixed-dose combination of efavirenz, emtricitabine and tenofovir disoproxil. It is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and adolescents weighing at least 35 kg.

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

4.3 Contraindications

Hypersensitivity to efavirenz, emtricitabine, tenofovir disoproxil or to any of the excipients listed in section 6.1.

Severe hepatic impairment (CPT, Class C) (see section 5.2).

Co-administration with *terfenadine, astemizole, midazolam, triazolam, pimozide, bepridil,* or *ergot alkaloids* (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine) because competition for cytochrome P450 (CYP) 3A4 by efavirenz could result in inhibition of metabolism and create the potential for serious and/or life-threatening adverse reactions (for example cardiac arrhythmias, prolonged sedation or respiratory depression) (see section 4.5).

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

Co-administration with *elbasvir* (EBR) and *grazoprevir* (GZR) due to the potential for significant decreases in plasma concentrations of EBR and GZR (see section 4.5).

Herbal preparations containing St. John´s wort (*Hypericum perforatum*) must not be used while taking [HA500 trade name] due to the risk of decreased plasma concentrations and reduced clinical effects of efavirenz (see section 4.5).

Co-administration with *voriconazole*. Efavirenz significantly decreases voriconazole plasma concentrations while voriconazole also significantly increases efavirenz plasma concentrations. Since [HA500 trade name] is a fixed-dose combination product, no dose adjustment of efavirenz is possible (see section 4.5).

Patients with:
- a family history of sudden death or of congenital prolongation of the QTc interval on electrocardiogram, or with any other clinical condition known to prolong the QTc interval.
- a history of symptomatic cardiac arrythmias or with clinically relevant bradycardia or with congestive cardiac failure accompanied by reduced left ventricle ejection fraction.
- severe disturbances of electrolyte balance e.g. hypokalaemia or hypomagnesaemia.

Patients taking medicines that are known to prolong the QTc interval (proarrhythmic).These include:
- antiarrhythmics of classes IA and III,
- neuroleptics, antidepressive agents,
- certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole and triazole antifungal agents,
- certain non-sedating antihistamines (terfenadine, astemizole),
- flecainide,
- certain antimalarials,
- methadone.

4.4 Special warnings and precautions for use

General

HBV antibody testing should be offered to all individuals before initiating therapy with emtricitabine and tenofovir disoproxil-containing therapies (see below “Patients with HIV and hepatitis B (HBV) or C virus (HCV) co-infection”).

Co-administration with other medicinal products

As a fixed combination, [HA500 trade name] should not be administered concomitantly with other medicinal products containing emtricitabine or tenofovir disoproxil, and should only be co-administered with products containing efavirenz when an increase in efavirenz dose is needed, e.g. in patients taking rifampicin (see section 4.2).

[HA500 trade name] should not be administered concomitantly with other cytidine analogues, such as lamivudine because of their similarities to emtricitabine. [HA500 trade name] should also not be administered concomitantly with medicinal products containing adefovir dipivoxil or tenofovir alafenamide.

No data are available on the safety and efficacy of [HA500 trade name] in combination with other antiretroviral agents.

Co-administration of [HA500 trade name] and didanosine is not recommended since exposure to didanosine is significantly increased following co-administration with tenofovir disoproxil (see section 4.5). Rarely, pancreatitis and lactic acidosis sometimes fatal have been reported.

Concomitant use of *Ginkgo biloba* extracts with [HA500 trade name] is not recommended (see section 4.5).

Co-administration with amodiaquine is not recommended since amodiaquine exposure significantly increased following co-administration with efavirenz. Hepatotoxicity has been observed (see section 4.5).

Antivirals against HCV

Co-administration with sofosbuvir/velpatasvir is not recommended, since plasma concentrations of velpatasvir significantly decreased due to CYP3A induction by efavirenz, which may result in loss of therapeutic effect of velpatasvir.

Co-administration of ledipasvir/sofosbuvir and efavirenz/emtricitabine/tenofovir disoproxil resulted in increased exposure to tenofovir and moderate reductions in ledipasvir exposure.
Tenofovir-associated adverse reactions should be monitored in patients receiving ledipasvir/sofosbuvir and [HA500 trade name].

Co-administration of glecaprevir/pibrentasvir with efavirenz may significantly decrease plasma concentrations of glecaprevir and pibrentasvir, leading to reduced therapeutic effect. Co-administration of glecaprevir/pibrentasvir with efavirenz is not recommended.

Co-administration with bedaquiline is not recommended, since plasma concentrations of bedaquiline decreased due to CYP3A induction by efavirenz, which may result in loss of therapeutic effect of bedaquiline (see section 4.5).

Switching from a PI-based antiretroviral regimen

Currently available data indicate a trend that in patients on a PI-based antiretroviral regimen the switch to a regimen consisting of efavirenz, emtricitabine and tenofovir disoproxil may lead to a reduction of the response to therapy (see section 5.1). These patients should be carefully monitored for rises in viral load and, since the safety profile of efavirenz differs from that of protease inhibitors, for adverse reactions.

Opportunistic infections

Patients receiving [HA500 trade name] or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by health care providers experienced in the treatment of patients with HIV associated diseases.

Liver disease

The pharmacokinetics, safety and efficacy of efavirenz/emtricitabine/tenofovir disoproxil 600mg/200mg/300mg tablets have not been established in patients with significant underlying liver disorders (see section 5.2).

[HA500 trade name] is contraindicated in patients with severe hepatic impairment (see section 4.3) and not recommended in patients with moderate hepatic impairment. Since efavirenz is principally metabolised by the CYP system, caution should be exercised when administering [HA500 trade name] to patients with mild hepatic impairment. These patients should be carefully monitored for efavirenz adverse reactions, especially nervous system symptoms. Laboratory tests should be performed to evaluate their liver disease at periodic intervals (see section 4.2).

Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy (CART) and should be monitored according to standard practice. If there is evidence of worsening liver disease or persistent elevations of serum transaminases to greater than 5 times the upper limit of the normal range, the benefit of continued therapy with [HA500 trade name] needs to be weighed against the potential risks of significant liver toxicity. In such patients, interruption or discontinuation of treatment must be considered (see section 4.8).

In patients treated with other medicinal products associated with liver toxicity, monitoring of liver enzymes is also recommended.

Liver toxicity

Hepatic failure has occurred in patients with no pre-existing hepatic disease or other identifiable risk factors, who were treated with efavirenz (see section 4.8). Liver enzyme monitoring should be considered for patients without pre-existing hepatic dysfunction or other risk factors.

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

Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions.

Healthcare providers should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with HBV.

In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant summary of product characteristics for these medicinal products.

The safety and efficacy of emtricitabine and tenofovir disoproxil have not been established for the treatment of chronic HBV infection. Emtricitabine and tenofovir individually and in combination have shown activity against HBV (see section 5.1). Limited clinical experience suggests that emtricitabine and tenofovir disoproxil have anti-HBV activity when used in antiretroviral combination therapy to control HIV infection.

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 appear to be self-limited. However, severe exacerbations, including fatalities, have been reported. Hepatic function should be monitored periodically with both clinical and laboratory follow-up for at least 6 months after discontinuation of hepatitis B therapy. If appropriate, resumption of hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

Liver flares are especially serious, and sometimes fatal, in patients with decompensated liver disease.

Psychiatric symptoms

Psychiatric adverse reactions have been reported in patients treated with efavirenz. Patients with a prior history of psychiatric disorders appear to be at greater risk of serious psychiatric adverse reactions. In particular, severe depression was more common in those with a history of depression. There have also been post-marketing reports of severe depression, death by suicide, delusions and psychosis-like behaviour. Patients should be advised that if they experience symptoms such as severe depression, psychosis or suicidal ideation, they should contact their health care provider immediately to assess the possibility that the symptoms may be related to the use of efavirenz, and if so, to determine whether the risk of continued therapy outweighs the benefits (see section 4.8).

Nervous system symptoms

Symptoms including, but not limited to, dizziness, insomnia, somnolence, impaired concentration and abnormal dreaming are frequently reported undesirable effects in patients receiving efavirenz in clinical studies. Dizziness was also seen in clinical studies with emtricitabine and tenofovir disoproxil. Headache has been reported in clinical studies with emtricitabine (see section 4.8).

Nervous system symptoms associated with efavirenz usually begin during the first one or two days of therapy and generally resolve after the first two to four weeks. Patients should be informed that if they do occur, these common symptoms are likely to improve with continued therapy and are not predictive of subsequent onset of any of the less frequent psychiatric symptoms.

Convulsions have been observed in patients receiving efavirenz, generally in the presence of a known medical history of seizures. Patients who are receiving concomitant anticonvulsant medicinal products primarily metabolised by the liver, such as phenytoin, carbamazepine and phenobarbital, may require periodic monitoring of plasma levels. In a drug interaction study, carbamazepine plasma concentrations were decreased when carbamazepine was co-administered with efavirenz (see section 4.5). Caution must be taken in any patient with a history of seizures.

Late-onset neurotoxicity, including ataxia and encephalopathy (impaired consciousness, confusion, psychomotor slowing, psychosis, delirium), may occur months to years after beginning efavirenz therapy.

Effects may be severe or life-threatening, but are generally reversible on discontinuation. Events of late-onset neurotoxicity have occurred in patients with CYP2B6 genetic polymorphisms at daily dosages of 600 mg of efavirenz and were associated with increased efavirenz plasma levels. Patients presenting with signs and symptoms of serious neurological adverse events should be evaluated promptly to assess the possibility that these events may be related to efavirenz use, and whether discontinuation of [HA500 trade name] is warranted.

QTc prolongation

QTc prolongation has been observed with the use of efavirenz. Consider alternatives to [HA500 trade name] for coadministration with a medicine with a known risk of QTc prolongation.

Renal function

[HA500 trade name] is not recommended for patients with moderate or severe renal impairment (creatinine clearance < 50 ml/min) or in patients requiring haemodialysis. Patients with moderate or severe renal impairment require a dose adjustment of emtricitabine and tenofovir disoproxil that cannot be achieved with this 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

Use of [HA500 trade name] should be avoided with concurrent or recent use of a nephrotoxic medicinal product. If concomitant use of [HA500 trade name] and nephrotoxic agents (e.g. aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir, interleukin-2) is unavoidable, renal function must be monitored weekly (see section 4.5).

Cases of acute renal failure after initiation of high dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs) have been reported in patients treated with tenofovir disoproxil and with risk factors for renal dysfunction. If [HA500 trade name] is co-administered with an NSAID, renal function should be monitored adequately.

If the creatinine test is routinely available, use the estimated glomerular filtration rate at baseline before initiating tenofovir disoproxil-containing regimens.

Benefits and risks should be carefully weighed when initiating therapy with [HA500 trade name] in patients at increased risk for renal toxicity, i.e. patients more than 50 years of age, with low body weight (<50 kg), diabetes, uncontrolled hypertension, renal failure, or concomitant use of boosted PIs or nephrotoxic drugs.

Creatinine testing during therapy is particularly advisable for high-risk patients to detect and limit further progression of renal impairment. If available, also serum phosphate should be measured in these patients.

If serum phosphate is < 1.5 mg/dl (0.48 mmol/l) or creatinine clearance is decreased to < 50 ml/min in any patient receiving emtricitabine and tenofovir disoproxil, renal function should be re-evaluated within one

week, including measurements of blood glucose, blood potassium and urine glucose concentrations (see section 4.8, proximal tubulopathy).
Consideration should also be given to interrupting treatment with tenofovir disoproxil in patients with creatinine clearance decreased to < 50 ml/min or decreases in serum phosphate below 1.0 mg/dl (0.32 mmol/l). Interrupting treatment with [HA500 trade name] 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 of [HA500 trade name] is indicated or where dose modification is necessary, separate preparations of efavirenz, emtricitabine and tenofovir disoproxil are available.

Elderly patients

Elderly patients are more likely to have decreased renal function; therefore caution should be exercised when treating elderly patients with tenofovir disoproxil.

Bone effects

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). If bone abnormalities are suspected then appropriate consultation should be obtained.

Tenofovir disoproxil may also cause a reduction in bone mineral density (BMD). In a controlled clinical study in adults decreases in bone mineral density of spine and changes in bone biomarkers from baseline were observed in both treatment groups, but were significantly greater in the tenofovir disoproxil treatment group than in the comparator group treated with stavudine (each in combination with lamivudine and efavirenz) at 144 weeks. Decreases in bone mineral density of the hip were significantly greater in this group until 96 weeks. However, there was no increased risk of fractures or evidence for clinically relevant bone abnormalities over 144 weeks.

In HIV-1 infected adolescents 12 years of age and older, the mean rate of bone gain was less in the tenofovir disoproxil-treated group compared to the placebo group. Skeletal growth (height) appeared to be unaffected. Markers of bone turnover in tenofovir disoproxil-treated adolescents suggest increased bone turnover, consistent with the effects observed in adults.

Osteonecrosis

Osteonecrosis has been reported, particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy. Their 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.

Rash

A mild-to-moderate rash very commonly develops within two weeks after starting efavirenz and does not require treatment discontinuation. The rash usually resolves within two weeks. Appropriate antihistamines and/or corticosteroids may improve tolerability and hasten the resolution of rash. Severe rash or erythema, including Stevens-Johnson syndrome, requires immediate discontinuation (see section 4.8). [HA500 trade name] is not recommended for patients who have had a life-threatening cutaneous reaction (e.g., Stevens-Johnson syndrome) while taking an NNRTI.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment.

For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Mitochondrial 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 (hyperlactataemia, 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 aetiology, particularly neurologic findings. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Immune Reactivation Syndrome

In HIV infected patients with severe immune deficiency at the time of institution of CART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment 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.

Effect of food

The administration [HA500 trade name] with food may increase efavirenz exposure (see section 5.2) and may lead to an increase in frequency of adverse reactions. It is recommended that [HA500 trade name] be taken on an empty stomach, preferably at bedtime.

Excipients

[HA500 trade name] contains a small amount of lecithin (soya) in the film-coat. This should be taken into consideration in patients with allergy to soya.

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 [HA500 trade name] contains efavirenz, emtricitabine and tenofovir disoproxil, any interactions that have been identified with these agents individually may occur with [HA500 trade name]. Interaction studies with these agents have only been performed in adults.

Interactions relevant to efavirenz

Efavirenz is eliminated through hepatic metabolism, mainly catalysed by the genetically polymorphic cytochrome (CYP) 450 isoform CYP2B6, but also by CYP3A. Therefore, agents that alter the activity of CYP2B6 or CYP3A may alter the plasma concentration of efavirenz.

Efavirenz is an *in vivo* inducer of CYP3A4, CYP2B6 and UGT1A1. Compounds that are substrates of these enzymes may have decreased plasma concentrations when co-administered with efavirenz. Efavirenz may be an inducer of CYP2C19 and CYP2C9; however, inhibition has also been observed *in vitro* and the net effect of co-administration with substrates of these enzymes is not clear (see section 5.2).

Efavirenz exposure may be increased when given with medicinal products (for example, ritonavir) or food (for example, grapefruit juice), which inhibit CYP3A4 or CYP2B6 activity. Compounds or herbal preparations (for example *Ginkgo biloba* extracts and St. John's wort) which induce these enzymes may give rise to decreased plasma concentrations of efavirenz. Concomitant use of St. John's wort is contraindicated (see section 4.3). Concomitant use of *Ginkgo biloba* extracts is not recommended (see section 4.4).

Efavirenz is contraindicated with concomitant use of medicines that may cause prolonged QTc interval and torsade de pointes, such as: antiarrhythmics of classes IA and III, neuroleptics and antidepressant agents, certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole, and triazole antifungal agents, certain non-sedating antihistaminics (terfenadine, astemizole), flecainide, certain antimalarials and methadone (see section 4.3).

Efavirenz should not be administered concurrently with terfenadine, astemizole, midazolam, triazolam, pimozide, bepridil or ergot derivatives, since this may result in altered plasma concentrations of these medicines (see section 4.3).

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

Interactions relevant to emtricitabine

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

There are no clinically significant interactions when emtricitabine is co-administered with indinavir, zidovudine, stavudine or famciclovir.

Emtricitabine is primarily excreted via glomerular filtration and active tubular secretion. With the exception of famciclovir and tenofovir disoproxil, the effect of co-administration of emtricitabine with medicinal products that are excreted by the renal route, or other medicinal products known to affect renal function, has not been evaluated. Co-administration of [HA500 trade name] with medicinal products that are eliminated by active tubular secretion may lead to an increase in serum concentrations of either emtricitabine or a co-administered medicinal product due to competition for this elimination pathway.

There is no clinical experience or virologic rationale for the co-administration of emtricitabine and cytidine analogues. Consequently, [HA500 trade name] should not be administered in combination with lamivudine for the treatment of HIV infection (see section 4.4).

Interactions relevant to tenofovir

Co-administration of tenofovir disoproxil and didanosine is not recommended (see section 4.4 and table of drug interactions below).

Renally eliminated medicinal products

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

Tenofovir disoproxil should be avoided with concurrent use of a nephrotoxic medicinal product, such as aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or 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.

Table of drug interactions for [HA500 trade name]

The drug interactions described are based on trials conducted with efavirenz, emtricitabine or tenofovir disoproxil as individual agents or are potential drug interactions; no drug interaction trials have been conducted using the fixed dose combination. The following list of interactions should not be considered exhaustive, but as representative of the classes of medicinal products where caution should be exercised (increased exposure is indicated as "↑", decreased exposure as "↓", no change as "↔", thrice daily as t.i.d., twice daily as "b.i.d.", and once daily as "q.d.").

Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration with [HA500 trade name]**
ANTI-INFECTIVES		
ANTIRETROVIRALS		
Nucleoside analogues		
Zidovudine **Stavudine** **Abacavir**	No interaction expected	
Abacavir / tenofovir disoproxil		Abacavir and [HA500 trade name] should not be co-administered, as the additive effect of abacavir is expected to be limited or absent.
Lamivudine / emtricitabine		Lamivudine and [HA500 trade name] should not be co-administered, due to the similarity between emtricitabine and lamivudine, and consequently expected lack of additive effects (see section 4.4.).
Didanosine (400 mg q.d.) / tenofovir disoproxil	Didanosine AUC ↑ 40-60%	The risk of didanosine-related adverse effects appears to be increased, and CD4 cells may decrease significantly on co-administration. Didanosine at 250 mg co-administered with tenofovir within several different antiretroviral combination regimens has been associated with a high rate of virological failure. Co-administration of [HA500 trade name] and didanosine is not recommended (see section 4.4).
Non-nucleoside inhibitors of reverse transcriptase		
Nevirapine **Etravirine**		Concomitant use not recommended because of

Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration with [HA500 trade name]**
		additive toxicity and no benefit in terms of efficacy.
Protease inhibitors		
Fosamprenavir/ritonavir (700/100 mg b.i.d)) / efavirenz	No clinically significant pharmacokinetic interaction	No dose adjustment necessary.
Saquinavir /ritonavir / efavirenz	Interaction not studied. For co-administration of efavirenz with low-dose ritonavir in combination with a protease inhibitor, see section on ritonavir above.	Insufficient data are available for making a dosing recommendation for saquinavir, with or without ritonavir, when co-administered with [HA500 trade name]. Co-administration with saquinavir, with or without ritonavir, is not recommended.
Indinavir / efavirenz	Indinavir AUC ↓ 31%, C_{trough} ↓ 40%	Insufficient data are available to make a dosing recommendation for indinavir when dosed with [HA500 trade name]. While the clinical significance of decreased indinavir concentrations has not been established, the magnitude of the observed pharmacokinetic interaction should be taken into consideration when choosing a regimen containing [HA500 trade name] and indinavir.
Indinavir/ritonavir (800/100 mg b.i.d.) / efavirenz	Indinavir AUCss ↓ 25%, C_{trough} ↓ 50%	Concomitant use with boosted indinavir is only recommended when it is possible to monitor the plasma concentration of indinavir.
Ritonavir (500 mg b.i.d) / efavirenz	Interaction studies have shown moderate increases in the AUC for both ritonavir and efavirenz.	Avoid concomitant use with full-dose ritonavir, due to low tolerability. When using [HA500 trade name] with low-dose ritonavir, the possibility of an increase in the incidence of efavirenz-associated adverse events should be considered, due to possible pharmacodynamic interaction.
Lopinavir/ritonavir soft capsules or oral solution / efavirenz	Substantial decrease in lopinavir exposure, necessitating dosage adjustment of lopinavir/ritonavir.	Insufficient data are available to make a dosing recommendation for

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration with [HA500 trade name]
Lopinavir/ritonavir tablets (400/100 mg b.i.d.) /efavirenz **(500/125 mg b.i.d.)** /efavirenz **Lopinavir/ritonavir (400 mg/100 mg b.i.d.)** /tenofovir disoproxil	When used in combination with efavirenz and two NRTIs, 533/133 mg lopinavir/ritonavir (soft capsules) twice daily yielded similar lopinavir plasma concentrations as compared to lopinavir/ritonavir (soft capsules) 400/100 mg twice daily without efavirenz (historical data). Lopinavir C_{min} ↓≈ 40% Lopinavir concentrations: similar to lopinavir/ritonavir 400/100 mg twice daily without efavirenz Lopinavir/ritonavir: No significant effect on lopinavir/ritonavir PK parameters. Tenofovir: AUC: ↑ 32% C_{max}: ↔ C_{min}: ↑ 51%	lopinavir/ritonavir when dosed with [HA500 trade name]. Co-administration of lopinavir/ritonavir and [HA500 trade name] is not recommended.
Atazanavir 400mg / efavirenz **Atazanavir** (400 mg q.d.)/ tenofovir disoproxil	Atazanavir AUCss ↓ 74%, C_{min} ↓ 93% Atazanavir: AUC: ↓ 25% C_{max}: ↓ 21% C_{min}: ↓ 40% Tenofovir: AUC: ↑ 24% C_{max}: ↑ 14% C_{min}: ↑ 22%	Concomitant use of [HA500 trade name] and unboosted atazanavir is not recommended.

Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration with [HA500 trade name]**
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) Co-administration of atazanavir/ritonavir with tenofovir disoproxil resulted in increased exposure to tenofovir. Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders.	Co-administration of atazanavir/ritonavir and [HA500 trade name] is not recommended.
Atazanavir/ritonavir / efavirenz (400 mg q.d./100 mg q.d./600 mg q.d., all administered with food)	Atazanavir: AUC: ↔* (↓ 9% to ↑ 10%) C_{max}: ↑ 17%* (↑ 8 to ↑ 27) C_{min}: ↓ 42%* (↓ 31 to ↓ 51)	
Atazanavir/ritonavir / efavirenz (400 mg q.d./200 mg q.d./600 mg q.d., all administered with food)	Atazanavir: AUC: ↔*/** (↓ 10% to ↑ 26%) C_{max}: ↔*/** (↓ 5% to ↑ 26%) C_{min}: ↑ 12%*/** (↓ 16 to ↑ 49) (CYP3A4 induction). * When compared to atazanavir 300 mg/ritonavir 100 mg q.d. in the evening without efavirenz. This decrease in atazanavir Cmin might negatively impact the efficacy of atazanavir. ** based on historical comparison.	
Tipranavir/ritonavir / efavirenz	Appropriate data on the interaction between the approved tipranavir regimen and efavirenz are lacking.	The combination of [HA500 trade name] and tipranavir/ritonavir should be avoided.
Darunavir/ritonavir (300/100 mg b.i.d) / efavirenz (600 mg q.d)	Darunavir AUC ↓ 13%, C_{min} ↓ 31%. Efavirenz AUC ↑ 21%, C_{min} ↑ 17%	[HA500 trade name] in combination with darunavir/ritonavir 800/100mg once daily may result in suboptimal darunavir Cmin. If [HA500 trade name] is to be used in combination with darunavir/ritonavir, the darunavir/ritonavir 600/100mg twice daily regimen should be used. Darunavir/ritonavir should be used with caution in combination with [HA500 trade name].

Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration with [HA500 trade name]**
Darunavir/ritonavir(300 mg/100 mg b.i.d.) / tenofovir disoproxil	Darunavir: No significant effect on darunavir/ritonavir PK parameters. Tenofovir: AUC: ↑ 22% C_{min}: ↑ 37%	Monitoring of renal function may be indicated, particularly in patients with underlying systemic or renal disease, or in patients taking nephrotoxic agents.
Darunavir/ritonavir/emtricitabine	Interaction not studied. No interaction expected.	
CCR-5 antagonists		
Maraviroc (100 mg b.i.d) / efavirenz 600 mg q.d	Maraviroc AUC: ↓ 45% Maraviroc C_{max}: ↓ 51% Efavirenz concentrations not measured, no effect is expected.	Refer to the Summary of Product Characteristics for the medicinal product containing maraviroc.
Integrase strand transfer inhibitors		
Raltegravir (400 mg single dose) / efavirenz Raltegravir (400 mg b.i.d.) / tenofovir disoproxil	Raltegravir AUC ↓ 36% Raltegravir AUC ↑ 49% Raltegravir C_{max} ↑ 64%	No dosage adjustment is necessary if [HA500 trade name] and raltegravir are co-administered.
ANTIVIRALS AGAINST HBV		
Adefovir dipivoxil / tenofovir disoproxil	AUC: ↔ C_{max}: ↔	[HA500 trade name] should not be administered concurrently with adefovir dipivoxil due to an expected lack of additive effect (see section 4.4).
Entecavir (1 mg q.d.)	AUC: ↔ C_{max}: ↔	No clinically significant pharmacokinetic interactions when [HA500 trade name] is co-administered with entecavir.
ANTIVIRALS AGAINST HCV		
Daclatasvir (60mg or 120 mg q.d.) **/** efavirenz	Daclatasvir AUC*: ↓ 32% C_{max}*: ↓ 17% C_{min}*: ↓ 59% Induction of CYP3A4 by efavirenz *results are dose-normalised to 60 mg dose.	The dose of daclatasvir should be increased to 90 mg once daily when coadministered with [HA500 trade name].
Daclatasvir (60mg)/ emtricitabine	No interaction expected	
Daclatasvir (60mg) / tenofovir disoproxil	No interaction observed	
Elbasvir/grazoprevir (50mg/200mg q.d.)/efavirenz	Elbasvir AUC ↓ 54% C_{max} ↓ 45%	Concomitant use with [HA500 trade name] is

Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration with [HA500 trade name]**
	C_{24} ↓ 59% Grazoprevir AUC ↓ 83% C_{max} ↓ 87% C_{24} ↓ 69% Efavirenz AUC ↔ C_{max} ↔ C_{24} ↔	contraindicated (see section 4.3).
Elbasvir/grazoprevir (50mg/200mg q.d.)/emtricitabine	No interaction observed	
Elbasvir/grazoprevir (50mg/200mg q.d.)/ tenofovir disoproxil	No interaction observed	
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + efavirenz/emtricitabine/tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)	Ledipasvir AUC: ↓ 34% C_{max}: ↓ 34% C_{min}: ↓ 34% Sofosbuvir AUC: ↔ C_{max}: ↔ GS-3310071 AUC: ↔ C_{max}: ↔ C_{min}: ↔ Efavirenz AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir AUC: ↑ 98% C_{max}: ↑ 79% C_{min}: ↑ 163%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4).
Sofosbuvir (400 mg q.d.) / efavirenz/emtricitabine/tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)	Sofosbuvir AUC: ↔ C_{max}: ↓ 19% GS-3310071 AUC: ↔ C_{max}: ↓ 23%	[HA500 trade name] and sofosbuvir can be co-administered without dose adjustment.

Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration with [HA500 trade name]**
	Efavirenz AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir AUC: ↔ C_{max}: ↑ 25% C_{min}: ↔	
Sofosbuvir/velpatasvir (400mg/100mg) / efavirenz/emtricitabine/tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)	Sofosbuvir AUC: ↔ C_{max}: ↑ 20% Velpatasvir AUC ↓ 53% C_{max} ↓ 47% C_{min} ↓ 57% Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir AUC ↑ 40 to 80% C_{max} ↑ 40 to 80%	Co-administration of [HA500 trade name] with sofosbuvir/velpatasvir is expected to decrease the concentration of velpatasvir. Co-administration with efavirenz-containing regimens is not recommended (see section 4.4).
ANTIFUNGALS		
Ketoconazole (400 mg single dose; efavirenz 600 mg to steady state) / efavirenz	Ketoconazole AUC ↓ 72%	Consider alternative antifungal agent, or use therapeutic drug monitoring (TDM) if available.
Itraconazole (200 mg b.i.d) / efavirenz	Itraconazole AUC at steady state ↓ 39%, C_{min} ↓ 44%	Consider alternative antifungal agent, or use TDM if available.
Posaconazole (400 mg b.i.d./400 mg q.d.) **/** efavirenz	Posaconazole: AUC ↓50% C_{max}↓ 45%	Concomitant use of posaconazole and efavirenz should be avoided.
Fluconazole (200 mg q.d) / efavirenz	No significant interaction	No dose adjustment is necessary.
Voriconazole (200 b.i.d) / efavirenz (600mg)	No data available	Efavirenz and voriconazole at standard doses must not be coadministered.

Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration with [HA500 trade name]**
Voriconazole (200 mg b.i.d.) / efavirenz (400 mg q.d)	Voriconazole AUCss: ↓ 77%; Efavirenz AUCss: ↑ 44%	The dose reduction for efavirenz with voriconazole at standard dose leads to a significant alteration in the pharmacokinetics of both drugs and must thus not be used.
Voriconazole (400 mg b.i.d) / efavirenz 300 mg q.d)	Voriconazole AUCss ↓ 7%; Efavirenz AUCss↑ 17%; both compared with standard doses of voriconazole and efavirenz (200 mg b.i.d and 600 mg q.d, respectively)	If coadministration is considered necessary, voriconazole should be dosed 400 mg b.i.d and efavirenz dosed at 300 mg q.d. As this dose reduction of efavirenz cannot be accommodated for with [HA500 trade name] alternative formulations of efavirenz, tenofovir disoproxil and emtricitabine should be used (see section 4.3).
ANTIBACTERIALS/ANTITUBERCULOTICS		
Clarithromycin (500 mg b.i.d, multiple doses) / efavirenz	Clarithromycin AUC ↓ 39%; 14-OH-clarithromycin AUC ↑ 34%	The clinical significance, if any, of these alterations in clarithromycin exposure is not known. A high frequency of rash was seen when the drugs were co-administered in healthy volunteers. Consider azithromycin instead, if possible**.**
Azithromycin (600 mg single dose) / efavirenz (400 mg once daily**),**	No clinically significant pharmacokinetic interaction	No dosage adjustment is necessary for either medicinal product.
Rifampicin (600 mg q.d, multiple doses) / efavirenz	Efavirenz AUC ↓ 26%, C_{min} ↓ 32%	When co-treating, a dose increase of efavirenz from 600 mg to 800 mg q.d. should be considered in patients weighing 50 kg or more. Individual tolerability and virological response should be considered when making the dose adjustment. No dose adjustment of rifampicin is recommended when given with [HA500 trade name].
Rifabutin (300 mg q.d) / efavirenz	Rifabutin AUCss ↓ 38%	Increase rifabutin dose by 50% if co-treating with [HA500 trade name].
ANTIMALARIALS		

Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration with [HA500 trade name]**
Atovaquone and proguanil Hydrochloride / efavirenz (250/100mg single dose/600mgq.d.) Atovaquone and proguanil hydrochloride/emtricitabine	Atovaquone: AUC: ↓ 75% (↓62 to ↓84) C_{max}: ↓44% (↓20 to ↓61) Proguanil: AUC: ↓43% (↓7 to ↓65) C_{max}: ↔	Concomitant administration of atovaquone/proguanil with [HA500 trade name] should be avoided whenever possible.
Atovaquone and proguanil hydrochloride/tenofovir disoproxil	Interaction not studied.	
Chloroquine **Proguanil** **Sulfadoxine** **Pyrimethamine** / efavirenz	No formal interaction studies available. Drug interactions and safety in coadministration with efavirenz has not been systematically evaluated; on a theoretical basis, clinically significant drug interactions with efavirenz are unlikely	
Mefloquine / efavirenz	Co-administration may decrease mefloquine exposure.	Use with caution.
Amodiaquine / efavirenz	Amodiaquine AUC ↑, possibly increased hepatic toxicity.	Co-administration is not recommended.
Quinine / efavirenz	No formal interaction study available. Quinine is extensively metabolised by CYP3A. Co-administration with efavirenz may decrease quinine exposure, and reduce the antimalarial effect.	If possible, an alternative agent to quinine should be used in co-treatment with [HA500 trade name].
Lumefantrine, Halofantrine / efavirenz	No formal interaction studies available. These agents are metabolised by CYP3A; hence, co-treatment with efavirenz may decrease exposure.	Co-treatment with [HA500 trade name] may decrease antimalarial efficacy. When co-treating caution is recommended.
Artemether/Lumefantrine / efavirenz (20/120 mg tablet, 6 doses of 4 tablets each over 3 days/600 mg q.d.)	Artemether: AUC: ↓ 51%; Cmax: ↓ 21% Dihydroartemisinin (active metabolite): AUC: ↓ 46%; Cmax: ↓ 38% Lumefantrine: AUC: ↓ 21%; Cmax: ↔; Efavirenz: AUC: ↓ 17%; Cmax: ↔ (CYP3A4 induction)	Co-treatment with [HA500 trade name] may decrease antimalarial efficacy. When co-treating caution is recommended.
ANTICONVULSANTS		
Carbamazepine (400 mg q.d) / efavirenz	Carbamazepine AUCss: ↓ 27%, C_{min} ↓ 35%; efavirenz AUCss: ↓ 36%, C_{min} ↓ 47%	Co-administration with [HA500 trade name] should be avoided unless plasma concentrations of carbamazepine and efavirenz can be monitored.

Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration with [HA500 trade name]**
Phenytoin / efavirenz	Co-administration may increase or decrease phenytoin and/or efavirenz concentrations.	Monitor the therapeutic response of phenytoin and increase dose if needed.
Valproic acid (250 mg b.i.d) / efavirenz	No significant interaction is likely.	
Vigabatrin	No significant interaction is likely	[HA500 trade name] and vigabatrin can be co-administered without dose adjustment.
ANTIDEPRESSANTS		
Selective Serotonin Reuptake Inhibitors (SSRIs)		
Sertraline / efavirenz (50 mg q.d./600 mg q.d.)	Sertraline: AUC: ↓ 39% C_{min}: ↓ 46% Efavirenz: AUC: ↔ C_{min}: ↔ (CYP3A4 induction)	When co-administered with [HA500 trade name] sertraline dose increases should be guided by clinical response.
CARDIOVASCULAR AGENTS		
Calcium channel blockers		
Diltiazem (240 mg q.d.) / efavirenz	Diltiazem: AUC: ↓ 69% Desacetyl diltiazem: AUC: ↓75% N-monodesmethyl diltiazem: AUC: ↓37%	Monitor the clinical effect of diltiazem and increase dose if necessary.
Verapamil, felodipine, nifedipine, nicardipine / efavirenz	Interaction not studied. Calcium channel blocker exposure is likely to be lowered in co-treatment with efavirenz.	Monitor clinical effect and increase calcium channel blocker dose if necessary.
LIPID LOWERING AGENTS		
Atorvastatin (10 mg q.d) / efavirenz	Atorvastatin: AUC: ↓ 43% Total active moiety: AUC: ↓34%	Cholesterol levels should be periodically monitored and the dose of atorvastatin increased in case of insufficient efficacy.
Pravastatin (40 mg q.d.) / efavirenz	Pravastatin: AUC: ↓ 40%	Cholesterol levels should be periodically monitored and the dose of pravastatin increased in case of insufficient efficacy.
Simvastatin 40 mg q.d.) / efavirenz	Simvastatin: AUC: ↓69% Total active moiety: AUC: ↓ 60%	Cholesterol levels should be periodically monitored and the dose of simvastatin increased in case of insufficient efficacy.
Rosuvastatin / efavirenz	Interaction not studied. Rosuvastatin is largely excreted unchanged via the faeces; therefore metabolic drug	

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration with [HA500 trade name]
	interaction with efavirenz is not expected.	
HORMONAL CONTRACEPTIVES / HRT		
Desogestrel (COC and POP), drospirenone (COC), norethisterone (POP and COC), norgestimate (COC) / efavirenz		Co-administration is not recommended.
Ethinylestradiol/norgestimate (0.035 mg + 0.25 mg q.d) / efavirenz	No change in ethinylestradiol exposure. Levonorgestrel AUC ↓ 83%, norelgestromin AUC ↓ 64% (active metabolites)	A reliable method of barrier contraception should be used in addition to oral contraceptives.
DMPA (medroxyprogesterone acetate, 150 mg i.m. single dose**) /** efavirenz	The pharmacokinetics and efficacy of DMPA was not altered due to co-treatment with efavirenz.	Because of the limited information available, a reliable method of barrier contraception must be used in addition to hormonal contraception.
Etonogestrel (implant and vaginal ring) / efavirenz	Interaction not studied. Decreased exposure of etonogestrel may be expected due to the CYP3A induction of efavirenz. There have been occasional postmarketing reports of contraceptive failure with etonogestrel in efavirenz-exposed patients.	A reliable method of barrier contraception must be used in addition to hormonal contraception.
Levonorgestrel (POP, COC and implants) / efavirenz	Levonorgestrel levels≈50%	Levonorgestrel implants are not recommended in women on long-term treatment with hepatic enzyme-inducing drugs such as efavirenz.
Ulipristal / efavirenz		Co-administration may decrease ulipristal exposure and thus reduce the efficacy of the emergency contraception pill. Non-hormonal emergency contraception (i.e. a copper intrauterine device (Cu-IUD)) should be considered.
Drospirenone HRT, dydrogesterone HRT, Estradiol, Levonogestrel HRT / efavirenz		Co-administration may decrease comedication exposure. Monitor for signs of hormone deficiency.
IMMUNOSUPPRESSANTS		
Tacrolimus **Cyclosporine** **Sirolimus** **/** efavirenz	Interaction not formally studied. Decreased exposure of these immunosuppressants may be	Dose adjustments of the immunosuppressants may be needed. Close monitoring of

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration with [HA500 trade name]
	expected when co-treating with efavirenz.	immunosuppressant drug concentrations for at least 2 weeks (until steady-state concentrations are reached) is recommended when starting or stopping therapy with [HA500 trade name].
OTHERS		
Methadone / efavirenz	Methadone AUC ↓ 52%	Monitor for withdrawal symptoms and increase methadone dose if necessary.
Buprenorphine / efavirenz	Buprenorphine AUC ↓ 50%; norbuprenorphine AUC ↓ 71% (active metabolite) Despite these decreases in exposure, no patients in the study exhibited withdrawal symptoms.	Monitor for withdrawal symptoms and increase buprenorphine dose if necessary.
Bupropion (150mg single dose -sustained release) **/** efavirenz	Bupropion: AUC: ↓55% C_{max}: ↓34% Hydroxybupropion: AUC: ↔ C_{max}: ↑50%	Increases in bupropion dosage should be guided by clinical response, but the maximum recommended dose of bupropion should not be exceeded. No dose adjustment is necessary for efavirenz.
Bupropion / emtricitabine	Interaction not studied.	
Bupropion / tenofovir disoproxil	Interaction not studied.	
Morphine / efavirenz	Co-administration may increase morphine concentrations	Monitor for signs of opioid toxicity.
Warfarin / efavirenz **Acenocoumarol /** efavirenz	No interaction study available Co-administration may decrease and less likely increase warfarin or acenocoumarol exposure.	Monitor INR. Dose adjustments of warfarin or acenocoumarol may be necessary.
Lorazepam (2mg single dose) / efavirenz	Lorazepam: AUC: ↑ 7%	No dose adjustment necessary.

Cannabinoid test interaction

Efavirenz does not bind to cannabinoid receptors. False-positive urine cannabinoid test results have been reported with some screening assays in uninfected and HIV-infected subjects receiving efavirenz. Confirmatory testing by a more specific method such as gas chromatography/mass spectrometry is recommended in such cases.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

Efavirenz

Studies of efavirenz in animals have shown reproductive toxicity (see section 5.3).

Data on the safety of efavirenz during pregnancy are reassuring, with no evidence of an increased risk of congenital anomalies with efavirenz compared with other antiretroviral medicines.

Tenofovir disoproxil and emtricitabine

Animal studies do not indicate any harmful effects of tenofovir disoproxil or emtricitabine with respect to pregnancy, fetal development, parturition or postnatal development (see section 5.3). In humans, the safety of tenofovir and emtricitabine in pregnancy has not been fully established. However, sufficient numbers of first trimester exposures have been monitored to detect at least a two fold increase in the risk of overall birth defects. No increase in birth defects was seen (www.apregistry.com).

The use of [HA500 trade name] may be considered during pregnancy.

Current recommendations on HIV and pregnancy (e.g. those from the WHO) should be consulted before advising patients on this matter.

Breastfeeding

Efavirenz, emtricitabine and tenofovir have been shown to be excreted in human milk. There is insufficient information on the effects of efavirenz, emtricitabine and tenofovir in newborns/infants. A risk to the breastfed 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 [HA500 trade name] are available. The effect of efavirenz on male and female fertility in rats has only been evaluated at doses that achieved systemic drug exposures equivalent to or below those achieved in humans given recommended doses of efavirenz. In these studies, efavirenz did not indicate harmful effects on fertility. Animal studies do not indicate harmful effects of emtricitabine or tenofovir disoproxil 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, dizziness has been reported during treatment with efavirenz, emtricitabine and tenofovir disoproxil. Efavirenz may also cause impaired concentration and/or somnolence. 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

Summary of the safety profile

The combination of efavirenz, emtricitabine and tenofovir disoproxil has been studied in 460 patients either as the fixed-dose combination tablet or as the component products. Adverse reactions were generally consistent with those seen in previous studies of the individual components. The most frequently reported adverse reactions with combined therapy with efavirenz, emtricitabine and tenofovir disoproxil among patients treated up to 48 weeks were psychiatric disorders (16%), nervous system disorders (13%), and gastrointestinal disorders (7%).

Severe skin reactions such as Stevens-Johnson syndrome and erythema multiforme, neuropsychiatric adverse reactions (including severe depression, death by suicide, psychosis-like behaviour, seizures), severe hepatic events, pancreatitis and lactic acidosis (sometimes fatal) have been reported.

Rare events of renal impairment, renal failure and proximal renal tubulopathy (including Fanconi syndrome) sometimes leading to bone abnormalities (infrequently contributing to fractures) have also been reported. Monitoring of renal function is recommended for patients receiving [HA500 trade name] (see section 4.4).

Discontinuation [HA500 trade name] therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis (see section 4.4).

The administration of [HA500 trade name] with food may increase efavirenz exposure and may lead to an increase in the frequency of adverse reactions (see section 5.2).

The following adverse events have been reported in controlled clinical trials during treatment of HIV-1 infection with efavirenz, emtricitabine and tenofovir disoproxil.

The adverse reactions from clinical studies and post-marketing experience are listed below by body system, organ class and absolute frequency.

Frequencies are defined as very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000).

Blood and lymphatic system disorders

Common:	neutropenia
Uncommon:	anaemia

Immune system disorders

Common:	allergic reaction
Uncommon:	hypersensitivity

Metabolic and nutrition disorders

Very common:	hypophosphataemia
Common:	hypertriglyceridaemia, hyperglycaemia
Uncommon:	hypercholesterolaemia, hypokalaemia
Rare:	lactic acidosis

Psychiatric disorders

Common:	abnormal dreams, anxiety and depression (severe in 1.6%), insomnia
Uncommon:	affect lability, aggression, confusional state, euphoric mood, hallucination, mania, paranoia, suicide attempt, suicidal ideation
Rare:	Neurosis*, delusion*, completed suicide*

Nervous system disorders

Very common:	headache, dizziness
Common:	cerebellar coordination and balance disturbances, disturbance in attention, somnolence
Uncommon:	agitation, amnesia, ataxia, abnormal coordination, convulsions, incoherent speech, tremor

Unknown:	encephalopathy

Eye disorders

Uncommon:	blurred vision

Ear and labyrinth disorders

Uncommon:	tinnitus, vertigo

Vascular disorders

Uncommon:	flushing

Gastrointestinal disorders

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

Hepatobiliary disorders

Common:	elevation of liver enzymes (ALT, AST, GGT), hyperbilirubinaemia
Uncommon:	acute hepatitis
Rare:	hepatic failure*, hepatic steatosis

Skin and subcutaneous tissue disorders

Very common:	rash (severe in <1%)
Common:	pruritus, urticaria, skin discolouration (increased pigmentation)
Uncommon:	angioedema, erythema multiforme, Stevens-Johnson syndrome
Rare:	photoallergic dermatitis

Musculoskeletal and connective tissue disorders

Very common:	elevated creatine kinase
Uncommon:	rhabdomyolysis, muscular weakness, myalgia
Rare:	osteomalacia (manifested as bone pain and infrequently contributing to fractures) (see section 4.4)*, myopathy

Renal and urinary disorders

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

Reproductive system and breast disorders

Uncommon:	gynaecomastia, libido decreased

Gastrointestinal disorders

Very common:	diarrhoea, vomiting, nausea
Common:	anorexia, dry mouth, abdominal pain, elevated serum lipase, elevated amylase including elevated pancreatic amylase, dyspepsia, flatulence, increased appetite
Uncommon:	pancreatitis

General disorders and administration site disorders

Very common:	asthenia
Common:	pain, fatigue

*These adverse reactions were identified through post-marketing surveillance for efavirenz, emtricitabine or tenofovir disoproxil. The frequency category was estimated from a statistical calculation based on the total number of patients treated with any of the components of this fixed dose combination.

Description of selected adverse reactions

Rash

In clinical trials of efavirenz, rashes were usually mild-to-moderate maculopapular skin eruptions that occurred within the first two weeks of initiating therapy with efavirenz. In most patients, rash resolved with continuing therapy with efavirenz within one month. [HA500 trade name] can be reinitiated in patients interrupting therapy because of rash. Use of appropriate antihistamines and/or corticosteroids is recommended when [HA500 trade name] is restarted.

Psychiatric symptoms

Serious psychiatric adverse reactions have been reported in patients treated with efavirenz, one of the components of [HA500 trade name].

Patients with a history of psychiatric disorders appear to be at greater risk of these serious psychiatric adverse reactions with frequencies ranging from 0.3% for manic reactions to 2.0% for both severe depression and suicidal ideation. There have also been post-marketing reports of death by suicide, delusions, psychosis-like behaviour and catatonia.

Nervous system symptoms

Nervous system symptoms are common with efavirenz, one of the components of [HA500 trade name]. In clinical studies of efavirenz, nervous system symptoms of moderate to severe intensity were experienced by 19% (severe 2%) of patients, and 2% of patients discontinued therapy due to such symptoms. They usually begin during the first one or two days of efavirenz therapy and generally resolve after the first two to four

weeks. They may occur more frequently when. Dosing without meals and at bedtime seems to improve the tolerability of these symptoms (see sections 4.2 and 5.2). Delayed neurotoxicity, sometimes severe, has also been reported in patients receiving efavirenz (see section 4.4) and may require treatment with [HA500 trade name] to be stopped.

Renal impairment

As [HA500 trade name] may cause renal damage, monitoring of renal function is recommended (see sections 4.4 and 4.8 Summary of the safety profile). Proximal renal tubulopathy generally resolved or improved after 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).

Renal tubulopathy

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy due to tenofovir disoproxil: rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), hypokalaemia, muscular weakness, myopathy and hypophosphataemia. These events are not considered to be causally associated with [HA500 trade name] in the absence of proximal renal tubulopathy.

Hepatic failure with efavirenz

Hepatic failure, including cases in patients with no pre-existing hepatic disease or other identifiable risk factors, as reported post-marketing, were sometimes characterised by a fulminant course, progressing in some cases to transplantation or death.

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.

Interaction with didanosine

Co-administration of [HA500 trade name] 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).

Bone effects of tenofovir disoproxil in adolescents

The effect of tenofovir disoproxil on bone mass in those not fully grown is a specific theoretical safety concern. Assessment of adverse reactions is based on one randomized trial in 87 HIV-1 infected paediatric subjects (12 to <18 years of age) who received treatment with tenofovir disoproxil (N=45) or placebo (N=42) in combination with other antiretroviral agents for 48 weeks. Bone effects observed in paediatric subjects 12 years of age and older, such as an increased bone turnover, were consistent with those observed in adult clinical trials (see section 4.4).

Immune Reactivation Syndrome

In HIV-infected patients with severe immune deficiency at the time of initiation of CART, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease) have also been reported; however, 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).

Special populations

Paediatric population

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

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

Undesirable effects in children taking efavirenz were generally similar to those of adult patients, however rash was reported more frequently in children.

[HA500 trade name] is not indicated for the treatment of children or adolescents weighing less than 35 kg.

Elderly

The combination of efavirenz, emtricitabine and tenofovir disoproxil has not been studied in patients over the age of 65. Older people are more likely to have decreased hepatic or renal function. Therefore caution should be exercised when treating older people with [HA500 trade name].

Patients with renal impairment

Since tenofovir disoproxil can cause renal toxicity, close monitoring of renal function is recommended in any patient with mild renal impairment treated with [HA500 trade name] (see sections 4.4 and 5.2).

HIV/HBV or HCV co-infected patients

Clinical studies included only a limited number of patients co-infected with HBV or HCV. The adverse reaction profile of efavirenz, 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 in this patient population, elevations in AST and ALT occurred more frequently than in the general HIV infected population.

Exacerbations of hepatitis after discontinuation of treatment

In HIV-infected patients co-infected with HBV, clinical and laboratory evidence of hepatitis may occur 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

Symptoms

Some patients accidentally taking efavirenz 600 mg twice daily have reported increased nervous system symptoms. One patient experienced involuntary muscle contractions.

Management

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.

Administration of activated charcoal may be used to aid removal of unabsorbed efavirenz. There is no specific antidote for overdose with efavirenz. Since efavirenz is highly protein bound, dialysis is unlikely to remove significant quantities of it from blood.

Up to 30% of the emtricitabine dose and approximately 10% of the tenofovir dose 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

Antivirals for treatment of HIV infections, combinations, ATC code: J05AR06

Mechanism of action and pharmacodynamic effect

Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. Efavirenz binds directly to reverse transcriptase and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by inducing a conformational change that causes a disruption of the enzyme's catalytic site. The activity of efavirenz does not compete with template or nucleoside triphosphates. HIV-2 reverse transcriptase and eukaryotic DNA polymerases (such as human DNA polymerases α, β, γ, or δ) are not inhibited by efavirenz.

Emtricitabine is an analogue of the nucleoside cytidine. Tenofovir disoproxil is converted *in vivo* to tenofovir, a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate. Emtricitabine and tenofovir are phosphorylated by cellular enzymes to form emtricitabine triphosphate and tenofovir diphosphate, respectively.

Emtricitabine triphosphate and tenofovir diphosphate competitively inhibit HIV-1 reverse transcriptase (RT), resulting in DNA chain termination. Both substances are active against HIV-1 and HIV-2, as well as against hepatitis B virus.

Both emtricitabine triphosphate and tenofovir diphosphate are weak inhibitors of mammalian DNA polymerases and there was no evidence of toxicity to mitochondria *in vitro* and *in vivo*.

Antiviral activity in vitro

Efavirenz demonstrated antiviral activity against most non-clade B isolates (subtypes A, AE, AG, C, D, F, G, J, and N) but had reduced antiviral activity against group O viruses. Emtricitabine displayed antiviral activity against HIV-1 clades A, B, C, D, E, F, and G. Tenofovir displayed antiviral activity against HIV-1 clades A, B, C, D, E, F, G, and O. Both emtricitabine and tenofovir showed strain specific activity against HIV-2 and antiviral activity against HBV.

In combination studies evaluating the *in vitro* antiviral activity of efavirenz and emtricitabine together, efavirenz and tenofovir together, and emtricitabine and tenofovir together, additive to synergistic antiviral effects were observed.

Resistance

The K65R mutation is selected *in vitro* when HIV-1 is cultured in the presence of increasing tenofovir concentrations. It may also emerge *in vivo* upon virological failure of a treatment regimen including tenofovir. K65R reduces tenofovir susceptibility *in vitro* approximately 2-fold, and has been associated with a lack of response to tenofovir-containing regimens. Clinical studies in treatment-experienced patients have assessed the anti-HIV activity of tenofovir against strains of HIV-1 with thymidine analogue mutations (TAMs), which are not selected for by tenofovir. Patients whose HIV expressed 3 or more TAMs that included either the M41L or L210W mutation showed reduced response to tenofovir.

HIV-1 resistance to emtricitabine develops as the result of the M184V mutation in the RT. This HIV-1 mutation was observed *in vitro* and in HIV-1 infected patients. Emtricitabine-resistant viruses were cross-resistant to lamivudine, but retained sensitivity to other nucleoside reverse transcriptase inhibitors (NRTIs)

(zidovudine, stavudine, tenofovir, abacavir, didanosine and zalcitabine), all non-nucleoside reverse transcriptase inhibitors (NNRTIs) and all protease inhibitors (PIs).

A large proportion of patients experiencing virological failure while receiving efavirenz will develop resistance to efavirenz. The main mutations occurring are K103N, G190S/A/E and Y188L; a single one of these mutations is sufficient to cause high-grade resistance. The cross resistance between efavirenz and nevirapine or delavirdine is extensive; therefore patients who have experienced virological failure with either of these drugs, are likely to harbour virus not susceptible to efavirenz, and vice versa. With an accumulating number of NNRTI mutations, the susceptibility to etravirine will also be compromised.

Due to the long half-life of efavirenz, a period of functional monotherapy with efavirenz may follow upon discontinuation of effective efavirenz-containing antiretroviral therapy. This may cause significant resistance, and compromise the efficacy of future efavirenz, nevirapine or delavirdine therapy (see section 4.4)

Clinical results

When tenofovir disoproxil and emtricitabine were combined with efavirenz in treatment-naïve adult 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 disoproxil 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.

No specific studies with the combination tenofovir disoproxil, emtricitabine and efavirenz have been conducted in adolescents.

Patients co-infected with HIV and HBV

Limited clinical experience in patients co-infected with HIV and HBV suggests that treatment with emtricitabine or tenofovir disoproxil in antiretroviral combination therapy to control HIV infection also results in a reduction in HBV DNA (3 log10 reduction or 4 to 5 $\log_{10}$ reduction, respectively) (see section 4.4).

5.2 Pharmacokinetic properties

The absorption characteristics of [HA500 trade name] have been determined after administration of 1 tablet in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	**Mean value ± standard deviation (*)**		
	Efavirenz	**Emtricitabine**	**Tenofovir**
Maximum concentration (C_{max})µg/ml	4.3 ± 1.5	1617 ± 446 (1561)	258 ± 96 (241)
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption µg.hour/ml	1984 ± 676 (1879)	9197 ± 2015 (8984)	1843 ± 534 (1770)
Time to attain maximum concentration (t_{max}) hour	50085 ± 20356 (46008)	2.1 ± 0.8	1.3 ± 0.7

*geometric mean

Pharmacokinetics of Efavirenz, Emtricitabine and Tenofovir disoproxil

	Efavirenz	**Emtricitabine**	**Tenofovir disoproxil**

<table>
<tr><td>General</td><td>NA</td><td>NA</td><td>Tenofovir disoproxil is a water-soluble ester prodrug, which is rapidly converted in vivo to tenofovir. Tenofovir is converted intracellularly to tenofovir monophosphate and to the active component, tenofovir diphosphate.</td></tr>
<tr><td colspan="4">Absorption</td></tr>
<tr><td>Absolute bioavailability</td><td>NA</td><td>75-93%</td><td>NA</td></tr>
<tr><td>Oral bioavailability</td><td>40% to 45%</td><td>NA</td><td>25% in fasted patients</td></tr>
<tr><td>Food effect</td><td><table><tr><td></td><td>$AUC_{(0-\infty)}$</td><td>C_{max}</td></tr><tr><td>High fat:</td><td>28%↑</td><td>79%↑</td></tr></table>Food increases absorption</td><td>Food does not affect absorption</td><td><table><tr><td></td><td>$AUC_{(0-\infty)}$</td><td>C_{max}</td><td>T_{max}</td></tr><tr><td>Light meal</td><td>No significant effect</td><td>No significant effect</td><td>No significant effect</td></tr><tr><td>High fat:</td><td>40%↑</td><td>14%↑</td><td>1h↑</td></tr></table>High fat meal increased oral bioavailability.</td></tr>
<tr><td colspan="4">Distribution</td></tr>
<tr><td>Volume of distribution (mean)</td><td>NA</td><td>After IV admin 1.4±0.3 L/kg</td><td>800 mL/kg</td></tr>
<tr><td>Plasma proteinbinding in vitro</td><td>99% (predominantly to albumin)</td><td>< 4%</td><td>< 0.7% (serum protein binding < 7.2%)</td></tr>
<tr><td>Tissue distribution</td><td>CSF: mean cerebrospinal fluid concentrations 0.69% of the corresponding plasma concentration for 1 month treatment.</td><td>Widely distributed in body
Mean plasma: blood concentration ratio=1.0
Mean semen:plasma concentration ratio=4.0</td><td>Well distributed, with highest concentrations in kidney and liver.</td></tr>
<tr><td colspan="2">Metabolism</td><td></td><td></td></tr>
<tr><td></td><td>hepatic metabolism metabolised by the cytochrome P450 system to hydroxylated metabolites followed by glucuronidation</td><td>oxidation of thiol moiety (approx 9% of dose) and glucuronic acid conjugation (approx 4% of dose)</td><td>In vitro studies have determined that neither tenofovir disoproxil nor tenofovir is a substrate for the CYP450 enzymes</td></tr>
<tr><td>Active metabolite(s)</td><td>None</td><td>None</td><td>Tenofovir</td></tr>
</table>

Elimination			
Elimination half life	52h after single dose and 40 – 55 h after multiple doses. Individuals with certain mutant CYP2B6 genotypes have a substantially prolonged terminal half life	Approximately 10 h Emtricitabine triphosphate: 39 h in intracellular peripheral blood mononuclear cells	12 to 18 hours. Tenofovir diphosphate: 10h in intracellular activated resting peripheral blood mononuclear cells and 50 hours in resting peripheral blood mononuclear cells
Mean systemic clearance (Cl/F)	NA	averaged 307 mL/min (4.03 mL/min/kg).	0.23 L/h/kg
% of dose excreted in urine	14 - 34% recovered in urine and < 1% excreted unchanged	approximately 86% recovered in urine 13% recovered in urine as three metabolites	70-80% as unchanged drug
% of dose excreted in faeces	NA	approximately 14%	NA
Pharmacokinetic linearity	In HV, less than dose proportional increase (dose range 100 – 1600 mg). In HIV infected patients, linear steady state pharmacokinetics (dose range 200 – 600 mg/day)	Linear pharmacokinetics (dose range 25 to 200 mg)	Linear pharmacokinetics (dose range 75 to 600 mg)
Drug interactions *(in vitro)*			
Transporters	NA	NA	Substrate of hOAT 1, hOAT3 and MRP 4
Metabolising Enzymes	CYP3A4 and CYP2B6 are the major isoenzymes responsible for efavirenz metabolism. Induces CYP3A4, CYP2B6 and UGT1A1 and possibly CYP2C19 and CYP2C9, although for CYP2C19 and 2C19 also inhibition is observed. Inhibits in vitro CYP3A4.also by CYP3A	No inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. No inhibition of UGT1A1	No significant inhibition ofCYP3A4, CYP2D6, CYP2C9, CYP2E1, or CYP1A1/2

NA = Not available

Special populations

Age

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

Gender

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

Ethnicity

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

Paediatric population

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

Renal impairment

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

Pharmacokinetic parameters were determined following administration of single doses of the individual preparations of emtricitabine 200 mg or tenofovir disoproxil 245 mg to non-HIV-infected patients with varying degrees of renal impairment. The degree of renal impairment was defined according to baseline creatinine clearance (normal renal function when creatinine clearance > 80 mL/min; mild impairment with creatinine clearance=50 to 79 mL/min; moderate impairment with creatinine clearance=30 to 49 mL/min and severe impairment with creatinine clearance=10 to 29 mL/min).

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

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

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

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

[HA500 trade name] is not recommended for patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min). Patients with moderate or severe renal impairment require dose interval adjustment of emtricitabine and tenofovir disoproxil that cannot be achieved with the combination tablet (see sections 4.2 and 4.4).

Hepatic impairment

The pharmacokinetics of the fixed dose combination of efavirenz, emtricitabine and tenofovir has not been studied in HIV infected patients with hepatic impairment. [HA500 trade name] should be administered with caution to patients with mild hepatic impairment (see sections 4.3 and 4.4).

[HA500 trade name] must not be used in patients with severe hepatic impairment (see section 4.3) and is not recommended for patients with moderate hepatic impairment. In a single-dose study of efavirenz, half-life was doubled in the single patient with severe hepatic impairment (Child-Pugh-Turcotte Class C), indicating a potential for a much greater degree of accumulation. A multiple-dose study of efavirenz showed no significant effect on efavirenz pharmacokinetics in patients with mild hepatic impairment (Child-Pugh-Turcotte Class A) compared with controls. There were insufficient data to determine whether moderate or severe hepatic impairment (Child-Pugh-Turcotte Class B or C) affects efavirenz pharmacokinetics.

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

A single 300 mg dose of tenofovir disoproxil was administered to non-HIV infected patients with varying degrees of hepatic impairment defined according to CPT classification. Tenofovir pharmacokinetics were not substantially altered in subjects with hepatic impairment suggesting that no dose adjustment of tenofovir disoproxil is required in these subjects.

5.3 Preclinical safety data

Efavirenz

Preclinical data revealed no special hazard for humans other than those observed in conventional studies of safety, pharmacology, repeated dose toxicity, and genotoxicity. In reproductive toxicology studies, malformations were observed in 3 of 20 fetuses/newborns from efavirenz-treated cynomolgus monkeys given doses resulting in plasma efavirenz concentrations similar to those seen in humans. Carcinogenicity studies showed an increased incidence of hepatic and pulmonary tumours in female mice, but not in male mice.

Emtricitabine

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

Tenofovir

Preclinical studies conducted in rats, dogs and monkeys revealed target organ effects in gastrointestinal tract, kidney, bone and a decrease in serum phosphate concentration. Bone toxicity was diagnosed as osteomalacia (monkeys) and reduced bone mineral density (rats and dogs). Findings in the rat and monkey studies indicated that there was a substance-related decrease in intestinal absorption of phosphate with potential secondary reduction in bone mineral density. 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 peripost 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 concentrations 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.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet:
Corn starch
Croscarmellose sodium
Hydroxypropyl cellulose
Hypromellose
Iron oxide red
Magnesium stearate
Microcrystalline cellulose
Sodium lauryl sulfate

Film coat:
Hypromellose
Iron oxide red
Iron oxide yellow
Lecithin (soya)
Polyvinyl alcohol (partially hydrolysed)
Talc
Titanium dioxide
Xanthan gum

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30°C. Protect from light. Store in a well closed container.

6.5 Nature and contents of container

Round, white opaque, induction-sealed 85cc HDPE bottles fitted with white polypropylene 38mm screw cap closures and containing one (1) silica gel desiccant bag of 3G.

Pack size: 30 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

Cipla Limited,
Cipla House, Peninsula Business Park,
Ganpatrao Kadam Marg, Lower Parel,
Mumbai 400 013,
India.

8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

HA500

9. DATE OF PREQUALIFICATION

08 December 2011

10. DATE OF REVISION OF THE TEXT

March 2023

References

General reference sources for this SmPC include

Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring. World Health Organization 2021, available at https://www.who.int/publications/i/item/9789240031593

European SmPC, Atripla, available at:
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000797/WC500028102.pdf

FDA label, Symfi, available at:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022142s000lbl.pdf

European SmPC, Sustiva, available at:
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000249/WC500058311.pdf

European SmPC, Epivir, available at:
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000107/WC500027572.pdf

European SmPC, Viread, available at:
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000419/WC500051737.pdf

Further references relevant to sections of the SmPC include:

Section 4.5

K.K. Scarsi, et al. Clin Infect Dis. (2016) 62 (6): 675-682 doi:10.1093/cid/civ1001

Weblinks accessed July 2022

Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/pqweb/medicines