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

[HA466 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains efavirenz 600 mg, lamivudine 300 mg and tenofovir disoproxil fumarate 300 mg (equivalent to tenofovir disoproxil 245 mg or tenofovir 136 mg)

Excipients with potential clinical effect

Each tablet contains 57 mg lactose (as monohydrate) and 43 mg of sodium. See section 4-4 for further information.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet.

White-coloured, capsule-shaped, film-coated tablets. They are biconvex (rounded on top and bottom) with a flat edge. The tablets have 'M 152' debossed on (stamped into) one side and are plain on the other side.

The tablets should not be divided.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[HA466 trade name] is indicated for the treatment of HIV-1 infection in patients 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

Treatment with [HA466 trade name] should be initiated by a health care provider experienced in the management of HIV-1 infection.

Posology

Patients weighing at least 35 kg

The recommended dose of [HA466 trade name] is 1 tablet taken orally once daily.

Patients less than 35 kg

[HA466 trade name] should not be used in children and adolescents weighing less than 35 kg.

Elderly

[HA466 trade name] should be administered with caution to elderly patients (see section 4.4).

Dose adjustments

Where discontinuation of therapy with one of the components of [HA466 trade name] is indicated or where dose modification is necessary, medicines containing the single active substances or other antiretroviral medicines may need to be used.

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

Renal impairment

[HA466 trade name] is not recommended for patients with moderate or severe renal impairment (creatinine clearance below 50 mL/minute). Patients with moderate or severe renal impairment require dose-interval adjustment of lamivudine and tenofovir disoproxil that cannot be achieved with the combination tablet (see sections 4.4 and 5.2).

Hepatic impairment

Patients with mild liver disease (Child-Turcotte-Pugh Class A) may be treated with the normal recommended dose. [HA466 trade name] is not recommended for patients with moderate or severe hepatic impairment because there are insufficient data to determine whether dose adjustment is necessary. (see sections 4.3, 4.4 and 5.2).

If [HA466 trade name] is discontinued in patients co-infected with HIV and hepatitis B virus, these patients should be closely monitored for evidence of exacerbation of hepatitis (see section 4.4).

Discontinuation of [HA466 trade name]

If therapy with [HA466 trade name] is discontinued, consideration should be given to the long half-life of efavirenz (see section 5.2) and long intracellular half-lives of tenofovir and lamivudine.

Missed dose and vomiting after a dose

It is important that the patient takes the medicine regularly as prescribed. Missing doses can increase the risk of resistance to [HA466 trade name] and reduce its effectiveness.

If the patient misses a dose and it is less than 12 hours after it was due, the patient should be advised to take the dose as soon as possible and then take the next dose at the scheduled time. If more than 12 hours have passed since the dose was due, the patient should omit the missed dose and take the next scheduled dose at the usual time. The patient should not take a double dose.

If the patient vomits within 1 hour of taking [HA466 trade name], the patient should take an extra dose. If vomiting occurs more than an hour after taking the dose, the patient does not need to take an extra dose and can take the next dose as usual when it is due.

Method of administration

[HA466 trade name] should be taken with water and swallowed whole. The tablets should be taken on an empty stomach (see sections 4.4 and 4.8).

To reduce adverse effects of efavirenz on the nervous system, bedtime dosing is recommended (see section 4.8).

4.3 Contraindications

Hypersensitivity to efavirenz, lamivudine or tenofovir disoproxil, or to any of the excipients contained in the formulation.

Severe hepatic impairment (Child-Turcotte-Pugh Class C) (see section 5.2).

Patients at risk of QTc interval prolongation including those with:

- a family history of sudden death or of congenital prolongation of the QTc interval, 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 hypomagnaesemia.

Co-administration of [HA466 trade name] with certain medicines is contraindicated (see section 4.5, under ‘Contraindicated combinations’).

4.4 Special warnings and precautions for use

Hepatitis B or C virus co-infection

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

Lamivudine and tenofovir disoproxil are also active against HBV. Therefore, discontinuation of [HA466 trade name] therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis. Patients co-infected with HIV and HBV who discontinue therapy must be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, hepatitis B therapy may be resumed.

Liver disease

[HA466 trade name] is contraindicated in patients with severe hepatic impairment (see section 4.3) and it is not recommended in patients with moderate hepatic impairment. Since efavirenz is principally metabolised by the CYP system, [HA466 trade name] should be used with caution in patients with mild hepatic impairment. These patients should be carefully monitored for efavirenz adverse reactions, especially for nervous system symptoms.

Patients with liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy (CART) and they 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.

In patients treated with other medicines 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.

Psychiatric symptoms

Psychiatric adverse reactions have been reported in patients treated with efavirenz. Patients with a 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 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 doctor immediately to assess the possibility of the symptoms being 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 dizziness, insomnia, somnolence, impaired concentration and abnormal dreams are frequently reported undesirable effects in patients receiving efavirenz. Dizziness was also seen with lamivudine and tenofovir disoproxil. Headache has been reported with lamivudine (see section 4.8).

Nervous system symptoms associated with efavirenz usually begin during the first 2 days of therapy and generally resolve after 2 to 4 weeks. Patients should be informed that these common symptoms are likely to resolve with continued therapy and are not predictive of subsequent onset of any of the less frequent psychiatric symptoms.

Convulsions have occurred in patients receiving efavirenz, generally in those with medical history of seizures. Patients who are receiving concomitant epilepsy medicines primarily metabolized by the liver, such as phenytoin, carbamazepine and phenobarbital, may require periodic monitoring of plasma levels. In a drug interaction study, carbamazepine plasma concentrations decreased when carbamazepine was co-administered with efavirenz (see section 4.5). [HA466 trade name] must be used with caution in any patient with a history of seizures. Some epilepsy medicines can interact with [HA466 trade name], see section 4.5.

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.

Patients presenting with signs and symptoms of serious neurological adverse events should be evaluated promptly to assess the possibility of these events being related to efavirenz use, and whether [HA466 trade name] should be discontinued.

QTc prolongation

QTc prolongation has been observed with the use of efavirenz, and this is of particular concern in homozygous carriers of the CYP2B6*6/*6 allele.

Concurrent use of [HA466 trade name] with other medicines that prolong the QTc interval (proarrhythmic) should be avoided (see section 4.5).

Renal effects

Lamivudine and tenofovir disoproxil are primarily excreted by the kidneys, through a combination of glomerular filtration and active tubular secretion.

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

Before starting [HA466 trade name], 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.

[HA466 trade name] is not recommended for patients with moderate or severe renal impairment (creatinine clearance less than 50 mL/minute). Patients with moderate or severe renal impairment require a dose adjustment of lamivudine and tenofovir disoproxil that cannot be achieved with the combination tablet (see sections 4.2 and 5.2).

Interrupting treatment should also be considered in case of progressive decline of renal function when no other cause has been identified. Where discontinuation of therapy with one of the components is indicated or where dose modification is necessary, separate preparations of efavirenz, lamivudine and tenofovir disoproxil are available.

This medicine should be avoided with concurrent or recent use of a nephrotoxic medicines (e.g. aminoglycosides, amphotericin B, cidofovir, foscarnet, ganciclovir, interleukin-2 medicines, pentamidine, vancomycin). If concomitant use of [HA466 trade name] and nephrotoxic agents is unavoidable, renal function must be monitored weekly (see section 4.5).

Acute renal failure has been reported after starting high dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs) in patients treated with tenofovir disoproxil and with risk factors for renal dysfunction. If [HA466 trade name] is co-administered with an NSAID, renal function should be monitored adequately.

Elderly patients

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

Rash

A mild to moderate rash very commonly develops within two 2 weeks after starting efavirenz and does not require treatment discontinuation. The rash usually resolves within two 2 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). [HA466 trade name] is not recommended for patients who have had a life-threatening cutaneous reaction (e.g., Stevens-Johnson syndrome) while taking an NNRTI.

Bone effects

Bone abnormalities such as osteomalacia, which can manifest as persistent or worsening bone pain and infrequently contribute to fractures, may be associated with tenofovir disoproxil-induced proximal renal tubulopathy. Tenofovir disoproxil may also reduce bone mineral density.

If bone abnormalities are suspected then an endocrinology or nephrology consultation should be sought.

Osteonecrosis

Osteonecrosis has been reported, particularly in patients with advanced HIV-disease and/or long-term exposure to combined antiretroviral therapy. Its etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression and 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.

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. Blood lipids and glucose should be monitored in line with HIV guidelines. Lipid disorders should be managed as clinically appropriate.

Mitochondrial dysfunction

Nucleoside and nucleotide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed *in utero* and/or postnatally to nucleoside analogues. The main adverse events reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactataemia, hyperlipasaemia). These events are often transitory. Late-onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently unknown. These findings should be considered for any child exposed in utero to nucleoside and nucleotide analogues, who presents with severe clinical findings of unknown 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

Immune reactivation syndrome has been reported in patients treated with combination antiretroviral therapy. During early stages of treatment, patients whose immune system responds to antiretroviral therapy may develop an inflammatory response to slow-developing or residual opportunistic infections (such as Mycobacterium avium infection, cytomegalovirus retinitis, Pneumocystis jirovecii pneumonia, or tuberculosis). These reactions may require further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, autoimmune hepatitis, polymyositis, and Guillain-Barré syndrome) have also been reported in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after starting antiretroviral treatment.

Opportunistic infections

Health care providers should tell patients with impaired immunity that opportunistic infections or other complications of HIV infection may still develop while receiving antiretroviral medicines. This risk reduces as the immune system recovers.

Pancreatitis

Treatment with [HA466 trade name] should be stopped immediately if clinical signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur (see section 4.8).

Effect of food

The administration of [HA466 trade name] with food may increase efavirenz exposure (see section 5.2) and increase the frequency of adverse reactions. It is recommended that [HA466 trade name] be taken on an empty stomach, preferably at bedtime.

Excipients

This medicine contains **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.

This medicinal product contains 43 mg **sodium** per tablet, equivalent to 2% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

4.5 Interaction with other medicinal products and other forms of interaction

No drug interaction studies have been performed using [HA466 trade name]. As this medicine contains efavirenz, lamivudine and tenofovir disoproxil, any interactions that have been identified with these agents individually may occur with this combination tablet. Interaction studies with these agents have only been performed in adults.

[HA466 trade name] should not be administered concomitantly with other medicinal products containing the components, efavirenz, lamivudine or tenofovir disoproxil. Due to similarities with lamivudine, this product should not be administered concomitantly with other cytidine analogues, such as emtricitabine. [HA466 trade name] should not be administered concomitantly with adefovir dipivoxil or with medicinal products containing tenofovir alafenamide.

The first table, below, lists interactions which have serious clinical consequences and the combination of [HA466 trade name] and the interacting medicines are **contraindicated**. The second table (grouped by therapeutic class) lists interactions which should be considered and, if necessary, concomitant administration should be avoided or adjustments made to the dose.

Efavirenz interactions

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

Efavirenz is an 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.

Efavirenz exposure may increase 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 decrease plasma concentrations of efavirenz.

Efavirenz can prolong the QT interval and this is of particular concern in homozygous carriers of the CYP2B6*6/*6 allele. Co-administration should therefore be avoided with other medicines that prolong QTc interval (see tables below).

Lamivudine and tenofovir disoproxil interactions

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

Renally eliminated medicinal products
Since lamivudine and tenofovir are primarily eliminated by the kidneys, co-administration of [HA466 trade name] with medicinal products that reduce renal function or compete for active tubular secretion (e.g. cidofovir) may increase serum concentrations of lamivudine, tenofovir and/or the co-administered medicinal products.

Use of [HA466 trade name] should be avoided with concurrent or recent use of a nephrotoxic medicine, such as an aminoglycoside, amphotericin B, cidofovir, foscarnet, ganciclovir, an interleukin-2 medicine, pentamidine or vancomycin and high-dose or prolonged use of non-steroidal anti-inflammatory drugs (NSAIDs).

Since tacrolimus can affect renal function, close monitoring is recommended when it is co-administered with tenofovir disoproxil.

Contraindicated combinations

Use of [HA466 trade name] with the following medicines can have serious clinical consequences and concomitant use is therefore **contraindicated**.

Contraindicated medicine	**Comment**
Amiodarone	Co-administration can potentiate the risk of severe QT-interval prolongation.
Amodiaquine	Efavirenz increases amodiaquine exposure with the risk of serious hepatic toxicity. Efavirenz also significantly decreases the plasma concentrations of amodiaquine active metabolite reducing its antimalarial activity.
Astemizole	Competition for CYP3A4 by efavirenz could inhibit metabolism of astemizole and thus increase the risk of serious and life-threatening adverse reactions.
Bepridil	Competition for CYP3A4 by efavirenz could inhibit metabolism of bepridil and thus increase the risk of serious or life-threatening adverse reactions.
Elbasvir/grazoprevir	Efavirenz significantly decreases plasma concentrations of elbasvir and grazoprevir which may lead to loss of virologic response to elbasvir/grazoprevir.
Ergot alkaloids (e.g. dihydroergotamine, ergonovine, ergotamine and methylergonovine)	Competition for CYP3A4 by efavirenz could inhibit metabolism of ergot alkaloids and thus increase the risk of serious or life-threatening adverse reactions.
Midazolam	Competition for CYP3A4 by efavirenz could inhibit metabolism of midazolam and thus increase the risk of serious or life-threatening adverse reactions.

Contraindicated medicine	Comment
Amiodarone	Co-administration can potentiate the risk of severe QT-interval prolongation.
Pimozide	Competition for CYP3A4 by efavirenz could inhibit metabolism of pimozide and thus increase the risk of serious or life-threatening adverse reactions.
St John's wort (*Hypericum perforatum*)	CYP3A4 induction by St John's work could decrease plasma concentrations of efavirenz, reducing its clinical effects.
Terfenadine	Competition for CYP3A4 by efavirenz could inhibit metabolism of terdenadine and thus increase the risk of arrhythmias prolonged sedation or respiratory sedation.
Triazolam	Competition for CYP3A4 by efavirenz could inhibit metabolism of triazolam and thus increase the risk of serious or life-threatening adverse reactions.
Voriconazole	Efavirenz significantly decreases voriconazole plasma concentrations while voriconazole significantly increases efavirenz plasma concentrations. Co-administration may potentiate the risk of QT-interval prolongation.

Other interactions to be considered

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 "↔").

Medicinal products by therapeutic areas	Interaction	Recommendations on co-administration with [HA466 trade name]
ANTI-INFECTIVES		
ANTIRETROVIRALS *In general, this product is intended to be a complete antiretroviral regimen. Nonetheless, drug-drug interactions with antiretrovirals are listed below to allow full access to all relevant information.*		
Nucleoside analogues		
Emtricitabine /lamivudine		Emtricitabine and [HA466 trade name] should not be co-administered, due to the similarity between emtricitabine and lamivudine, and consequently expected lack of additive effects.

Medicinal products by therapeutic areas	**Interaction**	**Recommendations on co-administration with [HA466 trade name]**
Didanosine / tenofovir disoproxil	Didanosine AUC ↑	Co-administration of [HA466 trade name] and didanosine is not recommended. The risk of didanosine-related adverse effects (e.g., pancreatitis, lactic acidosis) appears to be increased, and CD4 cells may decrease significantly on co-administration. Didanosine co-administered with tenofovir has been associated with a high rate of virological failure.
Non-nucleoside reverse transcriptase inhibitors		
NNRTIs / efavirenz		Concomitant use not recommended because of additive toxicity and no benefit in terms of efficacy.
Protease inhibitors		
Atazanavir/ritonavir / tenofovir disoproxil **Atazanavir/ritonavir** / efavirenz	Atazanavir ↓ Co-administration of atazanavir/ritonavir with tenofovir disoproxil increased exposure to tenofovir, thus increasing the risk of tenofovir-associated adverse events, including renal disorders.	Co-administration of atazanavir/ritonavir and [HA466 trade name] is not recommended.
Darunavir/ritonavir / efavirenz **Darunavir/ritonavir** / tenofovir disoproxil	Darunavir ↓ Efavirenz ↑ Tenofovir ↑	Darunavir/ritonavir should be used with caution in combination with [HA466 trade name]. The dose of darunavir/ritonavir may need to be adjusted to avoid suboptimal darunavir dose. Monitoring of renal function may be indicated, particularly in patients with underlying renal disease, or in patients taking nephrotoxic agents.
Lopinavir/ritonavir / efavirenz **Lopinavir/ritonavir** / tenofovir disoproxil	Lopinavir C_{min} ↓ Tenofovir: AUC: ↑ C_{max}: ↔ C_{min}: ↑	Co-administration of lopinavir/ritonavir and [HA466 trade name] is not recommended. Insufficient data are available to make a dosing recommendation for lopinavir/ritonavir when dosed with [HA466 trade name].
Ritonavir (500 mg b.i.d) / efavirenz (600 mg q.d)	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 efavirenz with low-dose ritonavir, the possibility of an increase in the incidence of efavirenz-associated adverse events should be considered.

Medicinal products by therapeutic areas	**Interaction**	**Recommendations on co-administration with [HA466 trade name]**
CCR-5 antagonists		
Maraviroc / efavirenz	Maraviroc AUC: ↓ C_{max}: ↓	The dose of maraviroc may need to be increased when co-administered with [HA466 trade name]; information on maraviroc should be consulted for further details since maraviroc also interacts with protease inhibitors.
Integrase strand transfer inhibitors		
Raltegravir / efavirenz **Raltegravir** / tenofovir disoproxil	Raltegravir AUC ↓ Raltegravir AUC ↑ Tenofovir AUC: ↓	[HA466 trade name] and raltegravir can be co-administered without dose adjustment.
ANTIVIRALS AGAINST HEPATITIS B VIRUS		
Adefovir dipivoxil / tenofovir disoproxil	AUC: ↔ C_{max}: ↔	[HA466 trade name] should not be administered concurrently with adefovir dipivoxil due to an expected lack of additive effect (see section 4.4).
ANTIVIRALS AGAINST HEPATITIS C VIRUS		
Daclatasvir / efavirenz	Daclatasvir ↓	The dose of daclatasvir should be increased to 90 mg once daily when co-administered with [HA466 trade name].
Glecaprevir/pibrentasvir / efavirenz	Glecaprevir ↓ Pibrentasvir ↓	Co-administration of glecaprevir/pibrentasvir with efavirenz is not recommended because it may lead to loss of virologic response to glecaprevir/pibrentasvir.
Ledipasvir/sofosbuvir efavirenz/emtricitabine/tenofovir disoproxil	Ledipasvir ↓ Sofosbuvir↔ Efavirenz ↔ Emtricitabine ↔ 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.
Sofosbuvir / efavirenz **Sofosbuvir** / tenofovir disoproxil	No clinically significant pharmacokinetic interaction No clinically significant pharmacokinetic interaction	No dose adjustment required for either medicinal product.

Medicinal products by therapeutic areas	**Interaction**	**Recommendations on co-administration with [HA466 trade name]**
Sofosbuvir/velpatasvir / efavirenz	Sofosbuvir AUC: ↔ C_{max}: ↑ Velpatasvir ↓	Co-administration of sofosbuvir/velpatasvir with efavirenz resulted in a reduction (approximately 50%) in the systemic exposure of velpatasvir. Co-administration with efavirenz-containing regimens is not recommended.
Sofosbuvir/ velpatasvir/ voxilaprevir / efavirenz	Velpatasvir ↓ Expected: Voxilaprevir ↓	Co-administration of sofosbuvir/velpatasvir/voxilaprevir and efavirenz is not recommended because it may result in loss of therapeutic effect of sofosbuvir/velpatasvir/voxilaprevir.
OTHER ANTIVIRALS		
Cidofovir / tenofovir disoproxil	Possible potentiation of renal toxicity	Co-administration of cidofovir and [HA466 trade name] should be avoided. If concomitant use is unavoidable, renal function should be monitored closely.
Foscarnet / tenofovir disoproxil	Possible potentiation of renal toxicity	Co-administration of foscarnet and [HA466 trade name] should be avoided. If concomitant use is unavoidable, renal function should be monitored closely.
Ganciclovir / tenofovir disoproxil	Possible potentiation of renal toxicity	Co-administration of ganciclovir and [HA466 trade name] should be avoided. If concomitant use is unavoidable, renal function should be monitored closely.
ANTIBACTERIALS/ANTITUBERCULOTICS		
Aminoglycosides / tenofovir disoproxil	Possible potentiation of renal toxicity	Co-administration of an aminoglycoside and [HA466 trade name] should be avoided. If concomitant use is unavoidable, renal function should be monitored closely.
Azithromycin / efavirenz	No clinically significant pharmacokinetic interaction. Co-administration may potentiate the risk of QT-interval prolongation.	No dosage adjustment is necessary for either medicinal product.
Clarithromycin / efavirenz	Clarithromycin AUC ↓ 14-OH-clarithromycin AUC ↑ Co-administration may potentiate the risk of QT-interval prolongation.	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.
Rifabutin / efavirenz	Rifabutin ↓	Increase rifabutin dose by 50% if co-treating with [HA466 trade name].
Rifampicin / efavirenz	Efavirenz ↓	When co-treating, a dose increase of efavirenz should be considered in patients

Medicinal products by therapeutic areas	**Interaction**	**Recommendations on co-administration with [HA466 trade name]**
		weighing 50 kg or more. Individual tolerability and virological response should be considered when making the dose adjustment.
Sulfadiazine / lamivudine	Co-administration has not been studied.	Potential renal toxicity. Monitor renal function closely.
Trimethoprim/sulfamethoxazole / lamivudine	Lamivudine: AUC ↑ Trimethoprim: AUC ↔ Sulfamethoxazole: AUC ↔	Patients should be monitored clinically. High doses of trimethoprim/sulfamethoxazole for treating *Pneumocystis jirovecii* pneumonia and toxoplasmosis have not been studied and should be avoided.
Vancomycin / tenofovir disoproxil	Possible potentiation of renal toxicity	Co-administration of vancomycin and [HA466 trade name] should be avoided. If concomitant use is unavoidable, renal function should be monitored closely.
ANTIFUNGALS		
Amphotericin B / tenofovir disoproxil	Possible potentiation of renal toxicity	Co-administration of amphotericin B and [HA466 trade name] should be avoided. If concomitant use is unavoidable, renal function should be monitored closely.
Fluconazole / efavirenz	No clinically significant interaction. Co-administration may potentiate the risk of QT-interval prolongation.	No dose adjustment is necessary.
Flucytosine / lamivudine	Potential for haematological toxicity.	Haematological parameters should be monitored, and dose reduction should be considered.
Itraconazole / efavirenz	Itraconazole ↓ Co-administration may potentiate the risk of QT-interval prolongation.	Consider alternative antifungal agent, or use therapeutic drug monitoring if available.
Ketoconazole / efavirenz	Ketoconazole ↓ Co-administration may potentiate the risk of QT-interval prolongation.	Consider alternative antifungal agent, or use therapeutic drug monitoring if available.
Posaconazole / efavirenz	Posaconazole: ↓ Co-administration may potentiate the risk of QT-interval prolongation.	Concomitant use of posaconazole and [HA466 trade name] should be avoided.

Medicinal products by therapeutic areas	**Interaction**	**Recommendations on co-administration with [HA466 trade name]**
ANTIMALARIALS		
Artemether/lumefantrine/efavirenz	Artemether: ↓ Dihydroartemisinin ↓ Lumefantrine: AUC: ↓ C_{max}: ↔ Efavirenz: AUC: ↓ C_{max}: ↔ Co-administration may potentiate the risk of QT-interval prolongation.	Co-treatment with [HA466 trade name] may decrease antimalarial efficacy. When co-treating caution is recommended.
Atovaquone and proguanil hydrochloride /efavirenz	Atovaquone: AUC: ↓ C_{max}: ↓ Proguanil: AUC: ↓ C_{max}: ↔	Concomitant administration of atovaquone/proguanil with [HA466 trade name] should be avoided.
Lumefantrine, halofantrine / efavirenz	No formal interaction studies available. These agents are metabolised by CYP3A; hence, co-treatment with efavirenz may decrease exposure. Co-administration may potentiate the risk of QT-interval prolongation.	Co-treatment with [HA466 trade name] may decrease antimalarial efficacy. When co-treating caution is recommended.
Mefloquine / efavirenz	Co-administration may decrease mefloquine exposure. Co-administration may potentiate the risk of QT-interval prolongation.	Use with caution.
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. Co-administration may potentiate the risk of QT-interval prolongation.	If possible, an alternative agent to quinine should be used in co-treatment with [HA466 trade name].
ANTHELMINTICS		
Praziquantel / efavirenz	Praziquantel AUC ↓	Concomitant use with efavirenz is not recommended due to significant decrease in

Medicinal products by therapeutic areas	Interaction	Recommendations on co-administration with [HA466 trade name]
	Efavirenz increases hepatic metabolism of praziquantel.	plasma concentrations of praziquantel, with risk of treatment failure. In case the combination is needed, an increased dose of praziquantel could be considered.
ANTICONVULSANTS		
Carbamazepine / efavirenz	Carbamazepine: ↓ Efavirenz: ↓	Co-administration with [HA466 trade name] should be avoided unless plasma concentrations of carbamazepine and efavirenz can be monitored.
Phenytoin, phenobarbital, and other anticonvulsants that are substrates of CYP isozymes / efavirenz	No interaction study available. Possible reduction or increase in the plasma concentrations of phenytoin, phenobarbital and other anticonvulsants that are substrates of CYP isozymes with efavirenz.	Co-administration should be avoided unless plasma concentrations of the anticonvulsants and efavirenz can be monitored.
Valproic acid / efavirenz	No clinically significant effect on efavirenz pharmacokinetics. Limited data suggest there is no clinically significant effect on valproic acid pharmacokinetics.	[HA466 trade name] and valproic acid can be co-administered without dose adjustment.
Vigabatrin, gabapentin / efavirenz	No significant interaction is likely.	No dose adjustment is necessary.
ANTICOAGULANTS		
Warfarin / efavirenz **Acenocoumarol**/efavirenz	No interaction study available. Co-administration may decrease (and less likely increase) warfarin exposure.	Monitor INR. Dose adjustments of warfarin or acenocoumarol may be necessary.
ANTIDEPRESSANTS		
Selective Serotonin Reuptake Inhibitors (SSRIs)		
Citalopram, escitalopram / efavirenz	Co-administration may potentiate the risk of QT-interval prolongation particularly in homozygous carriers of the CYP2B6*6/*6 allele.	The combination of [HA466 trade name] and citalopram or escitalopram should be avoided.

Medicinal products by therapeutic areas	**Interaction**	**Recommendations on co-administration with [HA466 trade name]**
Sertraline / efavirenz	Sertraline: AUC: ↓ C_{max}, C_{min}: ↓ Efavirenz: AUC: ↔ C_{max}: ↑ C_{min}: ↔	When co-administered with [HA466 trade name], sertraline dose increases should be guided by clinical response.
Norepinephrine and dopamine reuptake inhibitor		
Bupropion / efavirenz	Bupropion: AUC: ↓ C_{max}: ↓ Hydroxybupropion: AUC: ↔ C_{max}: ↑	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.
Tricyclic antidepressants		
Imipramine / efavirenz	Co-administration may potentiate the risk of QT-interval prolongation particularly in homozygous carriers of the CYP2B6*6/*6 allele.	The combination of [HA466 trade name] and imipramine should be avoided.
ANTIPSYCHOTICS		
Chlorpromazine / efavirenz	Co-administration may potentiate the risk of QT-interval prolongation particularly in homozygous carriers of the CYP2B6*6/*6 allele.	The combination of [HA466 trade name] and chlorpromazine should be avoided.
Haloperidol / efavirenz	Co-administration may potentiate the risk of QT-interval prolongation particularly in homozygous carriers of the CYP2B6*6/*6 allele.	The combination of [HA466 trade name] and haloperidol should be avoided.
Quetiapine / efavirenz	Co-administration may potentiate the risk of QT-interval prolongation particularly in homozygous carriers of	The combination of [HA466 trade name] and quetiapine should be avoided.

Medicinal products by therapeutic areas	Interaction	Recommendations on co-administration with [HA466 trade name]
	the CYP2B6*6/*6 allele.	
CARDIOVASCULAR MEDICINES		
Diltiazem / efavirenz	Diltiazem: ↓ Desacetyl diltiazem: ↓ N-monodesmethyl diltiazem: ↓	Monitor the clinical effect of diltiazem and increase dose if necessary.
Verapamil, felodipine, nifedipine, nicardipine / efavirenz	Interaction not studied. Exposure of a calcium channel blocker that is a substrate of CYP3A4 enzyme is likely to be lowered in co-treatment with efavirenz.	Monitor clinical effect and increase calcium channel blocker dose if necessary.
ANTIARRHYTHMICS		
Dronedarone, quinidine / efavirenz **Quinidine /** tenofovir disoproxil **Flecainide** /efavirenz	Tenofovir disoproxil ↑ Co-administration of efavirenz with medicines that may prolong the QT interval potentiate the risk of severe QT-interval prolongation, particularly in homozygous carriers of the CYP2B6*6/*6 allele.	Concomitant use with [HA466 trade name] is not recommended.
LIPID LOWERING AGENTS		
Atorvastatin / efavirenz	Atorvastatin: ↓ Total active moiety: ↓	Cholesterol levels should be periodically monitored and the dose of atorvastatin increased in case of insufficient efficacy.
Pravastatin / efavirenz	Pravastatin: ↓	Cholesterol levels should be periodically monitored and the dose of pravastatin increased in case of insufficient efficacy.
Simvastatin / efavirenz	Simvastatin: ↓ Total active moiety: ↓	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 interaction with efavirenz is not expected.	[HA466 trade name] can be co-administered with rosuvastatin without dose adjustment.

Medicinal products by therapeutic areas	Interaction	Recommendations on co-administration with [HA466 trade name]
HORMONAL CONTRACEPTIVES		
Depot medroxyprogesterone acetate (DMPA) / efavirenz	The pharmacokinetics and efficacy of DMPA was not altered due to co-treatment with efavirenz. However, in women with higher body weight who take efavirenz, it is predicted that clinically significant reduction of medroxyprogesterone levels may occur before 12 weeks, when the next depot medroxyprogesterone injection is due.	A reliable alternative method of contraception may be considered. In women with higher body weight who take [HA466 trade name], depot medroxyprogesterone acetate may be injected every 8–10 weeks instead of every 12 weeks.
Desogestrel (alone or in combined oral contraceptive), **drospirenone** (combined oral contraceptive), **norethisterone** (alone or in combined oral contraceptive), **norgestimate** (combined oral contraceptive) / efavirenz	Efavirenz is expected to reduce the contraceptive efficacy of oral contraceptives containing desogestrel, drospirenone, norethisterone and norgestimate.	Co-administration is not recommended.
Etonogestrel (implant) / 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 alternative method of contraception should be considered.
Levonorgestrel (alone, combined oral contraceptives and implants) /efavirenz	Co-administration of efavirenz with levonorgestrel can reduce levonorgestrel exposure and contraceptive failure has been reported with levonorgestrel-containing implants	A reliable alternative method of contraception should be considered.
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) should be considered.

Medicinal products by therapeutic areas	Interaction	Recommendations on co-administration with [HA466 trade name]
IMMUNOSUPPRESSANTS		
Ciclosporin, sirolimus, tacrolimus / efavirenz	Interaction not formally studied. Decreased exposure of these immunosuppressants may be expected (CYP3A4). These immunosuppressants are not anticipated to impact exposure of efavirenz.	Dose adjustments of the immunosuppressants may be needed. Close monitoring of immunosuppressant drug concentrations for at least 2 weeks (until steady-state concentrations are reached) is recommended when starting or stopping therapy with [HA466 trade name].
Tacrolimus / tenofovir disoproxil	Tacrolimus may affect renal function	Renal function should be monitored closely.
CANCER THERAPIES		
Aldesleukin (and other interleukin-2 medicines) / tenofovir disoproxil	Possible potentiation of renal toxicity	Co-administration of an interleukin-2 medicine and [HA466 trade name] should be avoided. If concomitant use is unavoidable, renal function should be monitored closely.
Cisplatin / lamivudine	Cisplatin and lamivudine could potentially compete for OCT2 which could slow their elimination. Also, cisplatin may impair renal function.	Potential renal toxicity. Monitor renal function closely.
Cladribine / lamivudine	Lamivudine inhibits intracellular phosphorylation of cladribine, leading to a risk of reduced cladribine efficacy.	Concomitant use of [HA466 trade name] with cladribine is not recommended.
Ifosfamide / tenofovir disoproxil	Potential renal additive toxicity.	Co-administration of tenofovir disoproxil should be avoided. If concomitant use is unavoidable, renal function should be monitored closely.
OTHERS		
Buprenorphine / efavirenz	Buprenorphine AUC ↓ norbuprenorphine AUC ↓ Efavirenz: No clinically significant pharmacokinetic interaction.	Monitor for withdrawal symptoms and increase buprenorphine dose if necessary.
***Ginkgo biloba* extracts** / efavirenz	Efavirenz ↓	Concomitant treatment is not recommended.
Methadone / efavirenz	Methadone AUC ↓	Monitor for withdrawal symptoms and increase methadone dose if necessary.

Medicinal products by therapeutic areas	Interaction	Recommendations on co-administration with [HA466 trade name]
	(CYP3A4 induction) Co-administration may potentiate the risk of QT-interval prolongation.	Monitor ECG for QT prolongation; risk is increased with higher methadone doses.
Morphine / efavirenz	Co-administration may increase morphine concentrations.	Monitor for signs of opioid toxicity.
Non-steroidal anti-inflammatory drugs (NSAIDs) / tenofovir disoproxil	Possible potentiation of renal toxicity.	Renal function should be monitored especially with long-term or high-dose use of an NSAID.
Pentamidine / tenofovir disoproxil	Possible potentiation of renal toxicity.	Co-administration of pentamidine and [HA466 trade name] should be avoided. If concomitant use is unavoidable, renal function should be monitored closely.
Sorbitol solution / lamivudine	Co-administration of sorbitol solution (3.2 g, 10.2 g, 13.4 g) with a single dose of lamivudine resulted in dose-dependent decreases in lamivudine exposure.	When possible, chronic co-administration of lamivudine with medicines containing sorbitol or other osmotic acting polyalcohols or monosaccharide alcohols (e.g. xylitol, mannitol, lactitol, maltitol) should be avoided. Consider more frequent monitoring of HIV-1 viral load, when chronic co-administration cannot be avoided.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

The use of [HA466 trade name] may be considered during pregnancy if clinically indicated.

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. Data on exposure in pregnant women indicate no malformative and fetal/neonatal effect associated with tenofovir disoproxil or lamivudine.

Studies of efavirenz in animals have shown reproductive toxicity. Animal studies do not indicate direct or indirect harmful effects of tenofovir disoproxil or lamuvidine with respect to reproductive toxicity (see section 5.3).

Breast-feeding

Efavirenz, lamivudine and tenofovir pass into breast milk.

Current recommendations on HIV and breast-feeding (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 clinical data on the effect of [HA466 trade name] are available. Animal studies do not indicate harmful effects of efavirenz, lamivudine or tenofovir disoproxil on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Dizziness has been reported during treatment with efavirenz 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 or operating machinery.

4.8 Undesirable effects

Severe skin reactions such as Stevens-Johnson syndrome and erythema multiforme, neuropsychiatric adverse reactions (including severe depression, 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.

Discontinuing [HA466 trade name] in patients co-infected with HIV and hepatitis B virus may be associated with severe acute exacerbations of hepatitis (see section 4.4).

The administration of [HA466 trade name] with food may increase efavirenz exposure and increase the frequency of adverse reactions (see section 5.2).

Tabulated summary of adverse reactions

The adverse events considered at least possibly related to the treatment are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common (at least 1 in 10), common (1 in 100 to 1 in 10), uncommon (1 in 1000 to 1 in 100), rare (1 in 10 000 to 1 in 1000), very rare (less than 1 in 10 000).

Blood and lymphatic system disorders	
Uncommon	neutropenia, anaemia, thrombocytopenia
Very rare	pure red cell aplasia
Immune system disorders	
Uncommon	hypersensitivity
Metabolism and nutrition disorders	
Very common	hypophosphataemia
Common	hypertriglyceridaemia
Uncommon	hypokalaemia, hypercholesterolaemia
Rare	lactic acidosis
Psychiatric disorders	
Common	abnormal dreams, anxiety, depression, insomnia
Uncommon	emotional lability, aggression, euphoric mood, hallucination, mania, paranoia, psychosis, suicide attempt, suicide ideation, catatonia
Rare	delusion, neurosis, completed suicide
Nervous system disorders	
Very common	dizziness
Common	cerebellar coordination and balance disturbances, disturbance in attention, headache, somnolence

Uncommon	agitation, amnesia, ataxia, abnormal coordination, confusional state, convulsions, abnormal thinking, tremor
Very rare	peripheral neuropathy (or paraesthesia)

Gastrointestinal disorders

Very common	diarrhoea, nausea, vomiting
Common	abdominal pain, abdominal distension, flatulence
Uncommon	pancreatitis
Rare	elevated serum amylase

Hepatobiliary disorders

Common	elevation of liver enzymes
Uncommon	acute hepatitis
Rare	hepatic failure, hepatic steatosis

Skin and subcutaneous tissue disorders

Very common	rash
Common	pruritus, hair loss
Uncommon	erythema multiforme, Stevens-Johnson syndrome
Rare	angioedema, photoallergic dermatitis

Musculoskeletal and connective tissue disorders

Common	arthralgia, muscle disorders, decreased bone mineral density
Uncommon	rhabdomyolysis, muscular weakness
Rare	myopathy, osteomalacia

Renal and urinary disorders

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

Respiratory, thoracic and mediastinal disorders

Common	cough, nasal symptoms

Eye disorders

Uncommon	blurred vision

Ear and labyrinth disorders

Uncommon	tinnitus, vertigo

Vascular disorders

Uncommon	flushing

Reproductive system and breast disorders

Uncommon	gynaecomastia

General disorders

Very common	asthenia
Common	fatigue, malaise, fever

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 2 weeks of initiating therapy with efavirenz. In most patients, rash resolved with continuing therapy with efavirenz within one month. [HA466 trade name] can be restarted in patients interrupting therapy because of rash. Use of an antihistamines or a corticosteroid, or both, is recommended when restarting [HA466 trade name].

Renal impairment

As [HA466 trade name] may cause renal damage, monitoring of renal function is recommended (see sections 4.4). Proximal renal tubulopathy generally resolved or improved after discontinuation of therapy. However, in some patients, declines in creatinine clearance did not completely resolve despite discontinuation.

Patients at risk of renal impairment, advanced HIV disease, or patients receiving concomitant nephrotoxic medications are at increased risk of incomplete recovery of renal function despite tenofovir disoproxil discontinuation (see section 4.4).

Renal tubulopathy

The following adverse reactions 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 the use efavirenz, lamivudine and tenofovir disoproxil in the absence of proximal renal tubulopathy.

Psychiatric symptoms

Patients with a history of psychiatric disorders appear to be at greater risk of serious psychiatric adverse reactions with efavirenz.

Nervous system symptoms

Nervous system symptoms are common with efavirenz. In clinical controlled 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 1 or 2 days of efavirenz therapy and generally resolve after the first 2 to 4 weeks.

Nervous system symptoms may occur more frequently when [HA466 trade name] is taken concomitantly with meals possibly due to increased efavirenz plasma levels (see section 5.2). Dosing at bedtime seems to improve the tolerability of these symptoms (see section 4.2 and 4.4).

Hepatic failure with efavirenz

Hepatic failure, including cases in patients with no pre-existing hepatic disease or other identifiable risk factors, was sometimes characterized by a fulminant course, progressing in some cases to transplantation or death.

Interaction with didanosine

Co-administration of [HA466 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.

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 decompensated liver disease or concomitant use of medicines that induce lactic acidosis, are at increased risk of severe or life-threatening lactic acidosis during tenofovir disoproxil treatment.

Metabolic parameters

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

Immune reactivation syndrome

In HIV-infected patients with severe immune deficiency at the time of initiation of combined antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease, autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Osteonecrosis

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combined antiretroviral therapy. The frequency of this is unknown.

Special populations

Paediatric patients

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

Reductions in bone mineral density (BMD) have been reported with tenofovir disoproxil in paediatric patients. In HIV-infected adolescents, the BMD Z-scores in subjects who received tenofovir disoproxil were lower than those in subjects who received placebo. In HIV-infected children, the BMD Z-scores in subjects who switched to tenofovir disoproxil were lower than those in subjects who remained on regimens containing stavudine or zidovudine.

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

Patients co-infected with HIV and hepatitis B or hepatitis C virus

Clinical studies included only a few patients co-infected with hepatitis B or hepatitis C virus. The adverse reaction profile of efavirenz, emtricitabine[‡] and tenofovir disoproxil in patients co-infected with HIV and either hepatitis B or hepatitis C virus was similar to that observed in patients infected with HIV without co-infection. However, as expected, 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 hepatitis B virus, clinical and laboratory evidence of hepatitis may occur after discontinuation of treatment (see section 4.4).

[‡] Based on a systematic review it is suggested that emtricitabine and lamivudine are pharmacologically equivalent and hence clinically interchangeable for therapy of HIV therap. Therefore, herein reference is made also to data obtained with emtricitabine.

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.

No specific symptoms or signs have been identified following acute overdose with lamivudine, apart from those listed as undesirable effects.

Treatment

If overdose occurs the patient must be monitored for toxicity (see sections 4.8), and standard supportive treatment applied as necessary.

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

Since lamivudine is dialysable, continuous haemodialysis could be used in the treatment of overdosage, although this has not been studied.

About 10% of the tenofovir dose can be removed by haemodialysis; the median haemodialysis clearance of tenofovir disoproxil is 134 mL/minute. It is not known whether peritoneal dialysis can remove tenofovir.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antivirals for treatment of HIV infections, combinations, ATC code: J05AR11

Mechanism of action and pharmacodynamic effects

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.

Lamivudine, the negative enantiomer of 2'-deoxy-3'-thiacytidine, is a dideoxynucleoside analogue. Tenofovir disoproxil is converted *in vivo* to tenofovir, a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate.

Lamivudine and tenofovir are phosphorylated by cellular enzymes to form lamivudine triphosphate and tenofovir diphosphate, respectively. Lamivudine triphosphate and tenofovir diphosphate competitively inhibit HIV-1 reverse transcriptase, resulting in DNA chain termination. Both substances are active against HIV-1 and HIV-2, as well as against hepatitis B virus.

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

The antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in T lymphoblastoid cell lines, primary monocyte/macrophage cells and PBMCs. The EC50 values for tenofovir

were in the range of 0.04-8.5 microM. Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC50 values ranged from 0.5-2.2 microM).

Resistance

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).

In many cases when a lamivudine-containing treatment regimen fails, the M184V mutation will be selected for at an early stage. M184V causes high-level resistance to lamivudine (>300-fold reduced susceptibility). Virus with M184V replicates less well than does wild type virus.

In-vitro data tend to suggest that the continuation of lamivudine in an antiretroviral regimen despite the development of M184V might provide residual anti-retroviral activity (likely through impaired viral fitness). The clinical relevance of these findings is not established.

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

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. The K65R mutation can also be selected by abacavir or didanosine and results in reduced susceptibility to these agents plus lamivudine, emtricitabine and tenofovir. The K65R mutation remains fully susceptible to efavirenz. In addition, a K70E substitution in HIV-1 RT has been selected by tenofovir and results in low-level reduced susceptibility to abacavir, emtricitabine, lamivudine and tenofovir.

Patients whose HIV expressed 3 or more TAMs that included either the M41L or L210W mutation showed reduced response to tenofovir.

Clinical results

Several clinical studies have confirmed the efficacy of the individual components of this fixed dose combination product. Efavirenz, lamivudine and tenofovir disoproxil were used as single entities in different combination regimens.

When tenofovir disoproxil and lamivudine were combined with efavirenz in treatment-naïve patients with HIV-1, the proportion of patients (ITT) with HIV-RNA <50 copies/ml were 79% and 68% at 48 and 144 weeks, respectively.

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

5.2 Pharmacokinetic properties

Absorption of [HA466 trade name]

The absorption characteristics of [HA466 trade name] have been determined after administration of a single dose tablet in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	Arithmetic mean value ± standard deviation (geometric mean)		
	Efavirenz	**Lamivudine**	**Tenofovir**
Maximum concentration (C_{max})	2689 ± 785 (2588) ng/mL	2483 ± 706 (2379) ng/mL	277 ± 79 (265) ng/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	64850 ± 21728 (61086) ng· h/mL	13457 ± 3717 (12916) ng· h/mL	2358 ± 627 (2268) ng·h/mL
Time to attain maximum concentration (tmax)	4.28 ± 1.61 h	1.92 ± 0.93 h	1.17 ± 0.57 h

Pharmacokinetics of efavirenz, lamivudine and tenofovir disoproxil

<table>
<tr><th></th><th>Efavirenz</th><th>Lamivudine</th><th>Tenofovir disoproxil</th></tr>
<tr><td>General</td><td>Peak efavirenz plasma concentrations are attained by 5 hours following single oral administration.</td><td>Following oral administration, peak lamivudine plasma concentrations are attained in about an hour.</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>NA</td><td>NA</td></tr>
<tr><td>Oral bioavailability</td><td>40% to 45%</td><td>80-85%</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>Co-administration of lamivudine with food results in a delay of T_{max} and a lower C_{max} (decreased by 47%). However, the extent (based on the AUC) of lamivudine absorbed is not influenced.</td><td><table><tr><td>$AUC_{(0-\infty)}$</td><td>C_{max}</td><td>T_{max}</td></tr><tr><td>35% ↑</td><td>15% ↑</td><td>45 min ↑</td></tr></table></td></tr>
<tr><td colspan="4">Distribution</td></tr>
<tr><td>Volume of distribution (mean)</td><td>NA</td><td>After IV admin 1.3 L/kg</td><td>800 mL/kg</td></tr>
<tr><td>Plasma protein-binding in vitro</td><td>>99% (predominantly to albumin)</td><td>< 36%</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>mean CSF:serum ratio=0.12.
The true extent of penetration or relationship with any clinical efficacy is unknown.</td><td>Well distributed throughout the body, with highest concentrations in kidney, liver and the intestinal contents.</td></tr>
</table>

Metabolism			
	Hepatic metabolism: metabolised by the cytochrome P450 system to hydroxylated metabolites followed by glucuronidation.	Only minor route (< 10%)	*In vitro* studies have determined that neither tenofovir disoproxil nor tenofovir is a substrate for the CYP450 enzymes.
Active metabolite(s)	None	None	Tenofovir
Elimination			
Elimination half life	52 h after single dose and 40–55 h after multiple doses. Individuals with certain mutant CYP2B6 genotypes have a substantially prolonged terminal half-life.	5 to 7 h lamivudine triphosphate: 16 to 19 h in the cell	12 to 18 h Tenofovir diphosphate: 10 h in intracellular activated resting peripheral blood mononuclear cells and 50 h in resting peripheral blood mononuclear cells.
Mean systemic clearance (Cl/F)	NA	Averaged 0.32 L/h/kg	0.23 L/h/kg
% of dose excreted in urine	14–34% recovered in urine and < 1% excreted unchanged.	Predominantly cleared unchanged by renal excretion.	70-80% as unchanged drug.
% of dose excreted in faeces	NA	NA	NA
Pharmacokinetic linearity	In healthy volunteers, 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	Linear pharmacokinetics (dose range 75 to 600 mg)
Drug interactions *(in vitro*)			
Transporters	NA	Substrate for OCT	Substrate of hOAT 1, hOAT3 and MRP 4
Metabolising enzymes	CYP3A4 and CYP2B6 are the major isoenzymes responsible for efavirenz metabolism. It induces CYP3A4, CYP2B6 and UGT1A1. It inhibits CYP3A4 in vitro.	No CYP3A substrate	No significant inhibition of CYP3A4, CYP2D6, CYP2C9, CYP2E1, or CYP1A1/2.

NA = Not available

Pharmacokinetics in special populations

Age and gender

Tenofovir exposure achieved in adolescent patients receiving oral daily doses of tenofovir disoproxil 245 mg was similar to exposures achieved in adults receiving once-daily doses of tenofovir disoproxil 245 mg.

Pharmacokinetic studies have not been performed in children or in the elderly (over 65 years) (see section 4.2).

There are no significant or clinically relevant gender differences in the pharmacokinetics of efavirenz, lamivudine and tenofovir. Limited data suggest that females may have higher exposure to efavirenz but they do not appear to be less tolerant of efavirenz.

Ethnicity

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

Renal impairment

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.

Pharmacokinetic parameters were determined following administration of single doses of the individual preparations of lamivudine 300 mg or tenofovir disoproxil 245 mg to non-HIV infected patients with varying degrees of renal impairment.

[HA466 trade name] is not recommended for patients with moderate or severe renal impairment (creatinine clearance less than 50 mL/minute). Patients with moderate or severe renal impairment require dose interval adjustment of lamivudine and tenofovir disoproxil that cannot be achieved with the combination tablet (see sections 4.2 and 4.4).

Hepatic impairment

[HA466 trade name] should be administered with caution to patients with mild hepatic impairment (see sections 4.3 and 4.4).

[HA466 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-Turcotte-Pugh 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-Turcotte-Pugh Class A) compared with controls. There were insufficient data to determine whether moderate or severe hepatic impairment (Child-Turcotte-Pugh Class B or C) affects efavirenz pharmacokinetics.

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

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

Lamivudine

Non-clinical data on lamivudine reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, carcinogenic potential and toxicity to reproduction and development. Lamivudine was not mutagenic in bacterial tests, but showed activity in an *in vitro* cytogenetic assay and the mouse lymphoma assay. Lamivudine was not genotoxic *in vitro* at doses that gave plasma concentrations around 40-50 times higher than the anticipated clinical plasma levels. Based on the totality of the available data it is concluded that lamivudine should not represent a genotoxic hazard to patients undergoing treatment.

Tenofovir

Non-clinical safety pharmacology studies on tenofovir disoproxil reveal no special hazard for humans.

Studies conducted in rats, dogs and monkeys revealed target organ effects in kidney, bone and a decrease in serum phosphate concentration.

Bone toxicity was diagnosed as osteomalacia (monkeys) and reduced bone mineral density (rats and dogs). Bone toxicity in young adult rats and dogs occurred at exposures ≥ 5-fold the exposure in paediatric or adult patients; bone toxicity occurred in juvenile infected monkeys at very high exposures following subcutaneous dosing (≥ 40-fold the exposure in patients). 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 for these toxicities.

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

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

Tenofovir disoproxil did not show any carcinogenic potential in a long-term oral carcinogenicity study in rats. A long-term oral carcinogenicity study in mice showed a low incidence of duodenal tumours, considered likely related to high local 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet
Croscarmellose sodium
Hydroxypropyl cellulose
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose
Sodium chloride
Sodium lauryl sulphate

Film coat
Polyethylene glycol 3350
Polyvinyl alcohol (partially hydrolysed)
Talc
Titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Round, opaque white plastic (HDPE) bottle containing 30 or 90 tablets. It also contains a canister of 2 g of desiccant (drying material). The bottle has an aluminium/plastic foil seal and an opaque white plastic (polypropylene) screw cap.

Round, opaque blue, plastic (HDPE) bottle containing 30 or 90 tablets. It also contains a canister of 2 g of desiccant (drying material). The bottle has an aluminium/plastic foil seal and an opaque blue plastic (polypropylene) screw cap.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7. SUPPLIER

Mylan Laboratories Limited
Plot No. 564/A/22, Road No.92, Jubilee Hills
Hyderabad - 500096, Telengana
India
Email: ProductSafety@viatris.com

8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

HA466

9. DATE OF PREQUALIFICATION

25 October 2010

10. DATE OF REVISION OF THE TEXT

July 2026

References

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

Sustiva 600 mg film-coated tablets: summary of product characteristics. European Medicines Agency, 14 March 2024, available at: https://www.ema.europa.eu/en/documents/product-information/sustiva-epar-product-information_en.pdf

Epivir 150 mg and 300 mg film-coated tablets: summary of product characteristics. European Medicines Agency, 29 August 2022, available at: https://www.ema.europa.eu/en/documents/product-information/epivir-epar-product-information_en.pdf

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Symfi: highlights of prescribing information. U.S. Food and Drug Administration; October 2019, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/022142s037lbl.pdf

Further references relevant to sections of the SmPC include:

Sections 4.5 & 4.6

University of Liverpool Drug Interactions websites: http://hiv-druginteractions.org/

Efavirenz: Drug and Lactation Database. National Library of Medicine; 15 July 2025 (https://www.ncbi.nlm.nih.gov/books/NBK501534)

Tenofovir: Drug and Lactation Database. National Library of Medicine; 15 November 2025 (https://www.ncbi.nlm.nih.gov/books/NBK501549)

Lamivudine: Drug and Lactation Database. National Library of Medicine; 15 December 2025 (https://www.ncbi.nlm.nih.gov/books/NBK501536/)

All references last accessed in April 2026

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