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

[HA562 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 600 mg efavirenz, 200 mg emtricitabine and 300 mg tenofovir disoproxil fumarate (TDF) equivalent to 245 mg of tenofovir disoproxil or 136 mg of tenofovir.

For full list of excipients see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablets

[HA562 trade name] is pink, capsule-shaped, film-coated tablets. They are biconvex (rounded on top and bottom) with a bevelled edge. The tablets have "CL 81" debossed (Stamped into) on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[HA562 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 [HA562 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 [HA562 trade name] is 1 tablet taken orally once a day.

Patients weighing less than 35 kg

[HA562 trade name] is not recommended for use in children or adolescents weighing less than 35 kg, as dose adjustments are necessary that cannot be achieved with this fixed-dose combination.

Elderly

[HA562 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 [HA562 trade name] is indicated or where dose modification is necessary, medicines containing the single active substance or other antiretroviral medicines may need to be used.

Renal impairment

[HA562 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

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

adjustment of emtricitabine and tenofovir disoproxil that cannot be achieved with the combination tablet (see sections 4.4 and 5.2).

Hepatic impairment

The pharmacokinetics of [HA562 trade name] has not been studied in patients with hepatic impairment. Patients with mild liver disease (Child-Turcotte-Pugh Class A) may be treated with the normal recommended dose of [HA562 trade name] (see sections 4.3, 4.4 and 5.2).

If [HA562 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 [HA562 trade name]

If therapy with [HA562 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 emtricitabine.

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 [HA562 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 [HA562 trade name], the patient should take another 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

[HA562 trade name] should be swallowed whole with water. 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, emtricitabine, tenofovir disoproxil or to any of the excipients listed in section 6.1.

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 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.

Co-administration of [HA562 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).

Tenofovir disoproxil is indicated for the treatment of HBV and emtricitabine has shown activity against HBV in pharmacodynamic studies. Discontinuation of [HA562 trade name] in HBV-infected patients may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue [HA562 trade name] should 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

[HA562 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, [HA562 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 and they 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 [HA562 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 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 health care provider 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 in patients receiving efavirenz. Dizziness was also seen with emtricitabine and tenofovir disoproxil. Headache has been reported with emtricitabine (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 a history of seizures. Patients who are receiving concomitant epilepsy medicines 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 decreased when carbamazepine was co-administered with efavirenz (see section 4.5). [HA562 trade name] must be used with caution in any patient with a history of seizures. Some epilepsy medicines can interact with [HA562 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 therapy with efavirenz. 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 with signs and symptoms of serious neurological adverse events should be evaluated promptly to assess if these events are related to efavirenz, and whether [HA562 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 [HA562 trade name] with other medicines that prolong the QTc interval (proarrhythmic) should be avoided (see section 4.5).

Renal effects

Emtricitabine and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. Less than 1% of the efavirenz dose is excreted unchanged in the urine and renal impairment has minimal effect on the elimination of efavirenz.

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 [HA562 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.

[HA562 trade name] is not recommended for patients with moderate or severe renal impairment (creatinine clearance less than 50 mL/minute) 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).

During treatment, if serum phosphate is less than 1.5 mg/dL (0.48 mmol/L) or creatinine clearance drops below 50 mL/minute, renal function should be re-evaluated within 1 week, including measurements of blood glucose, blood potassium and urine glucose concentrations (see section 4.8, proximal tubulopathy). Interruption of tenofovir disoproxil treatment should be considered if creatinine clearance has decreased below 50 mL/minute or serum phosphate below 1.0 mg/dL (0.32 mmol/L). Interrupting treatment with [HA562 trade name] should also be considered in case of progressive decline of renal function when no other cause has been identified.

Use of [HA562 trade name] should be avoided with concurrent or recent use of a nephrotoxic medicine (e.g. aminoglycosides, amphotericin B, cidofovir, foscarnet, ganciclovir, interleukin-2 medicines, pentamidine, vancomycin). If concomitant use of [HA562 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 [HA562 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, medicines containing emtricitabine and tenofovir disoproxil should be used with caution in elderly patients.

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 or long-term exposure to combined antiretroviral therapy. Its aetiology 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.

Rash

A mild to moderate rash very commonly develops within 2 weeks after starting efavirenz and does not require treatment discontinuation. The rash usually resolves within 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). [HA562 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 lifestyle. For lipids, there is some evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any treatment. Blood lipids and glucose should be monitored in line with HIV guidelines. Lipid disorders should be managed as clinically appropriate.

Mitochondrial dysfunction following exposure in utero

Nucleoside and nucleotide analogues may affect 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 nucleoside or nucleotide analogues 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 [HA562 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 [HA562 trade name] with food may increase efavirenz exposure (see section 5.2) and increase the frequency of adverse reactions. It is recommended that [HA562 trade name] be taken on an empty stomach, preferably at bedtime.

4.5 Interaction with other medicinal products and other forms of interaction

As [HA562 trade name] contains efavirenz, emtricitabine and tenofovir disoproxil, any interactions that have been identified with these agents individually may occur with [HA562 trade name]. Interaction studies with these agents have only been performed in adults.

[HA562 trade name] should not be administered with any other medicines containing adefovir dipivoxil, emtricitabine, lamivudine, tenofovir alafenamide, or tenofovir disoproxil.

The first table, below, lists interactions which have serious clinical consequences and the combination of [HA562 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 medicines (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 has been shown to 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).

Emtricitabine interactions

In vitro and clinical pharmacokinetic interaction studies have shown that the potential for CYP-mediated interactions involving emtricitabine with other medicine is low. Co-administration of emtricitabine with medicines that are eliminated by active tubular secretion may increase concentrations of emtricitabine or the

co-administered medicinal product, or both. Medicines that decrease renal function may increase concentrations of emtricitabine.

Tenofovir disoproxil interactions

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

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

Tenofovir disoproxil should be avoided with concurrent use of a nephrotoxic medicine, such as an aminoglycoside, amphotericin B, cidofovir, foscarnet, ganciclovir, an interleukin-2 medicine, pentamidine, or vancomycin (see section 4.4).

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

Contraindicated combinations

Use of [HA562 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.
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.

Contraindicated medicine	Comment
Amiodarone	Co-administration can potentiate the risk of severe QT-interval prolongation.
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 concerning co-administration with [HA562 trade name]
ANTI-INFECTIVES		
ANTIRETROVIRALS		
Nucleoside analogues		
Abacavir / tenofovir disoproxil		Abacavir and [HA562 trade name] should not be co-administered, as the additive effect of abacavir is expected to be limited or absent.
Lamivudine / emtricitabine		Lamivudine and [HA562 trade name] should not be co-administered, due to the similarity between emtricitabine and lamivudine, and consequently expected lack of additive effects.
Didanosine / tenofovir disoproxil	Didanosine AUC ↑	Co-administration of [HA562 trade name] and didanosine is not recommended. The risk of didanosine-related adverse effects 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 inhibitors of reverse transcriptase		
NNRTIs / efavirenz		Co-administration of [HA562 trade name] and another NNRTI is not recommended. Use of two NNRTIs does not increase efficacy and may increase side effects.

Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration with [HA562 trade name]**
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. Efavirenz may decrease trough concentration of atazanavir and thereby reduce efficacy.	Co-administration of atazanavir/ritonavir and [HA562 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 [HA562 trade name]. The dose of darunavir/ritonavir may need to be adjusted to avoid suboptimal darunavir dose. Renal function may need monitoring, particularly in patients with underlying systemic or 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 [HA562 trade name] is not recommended. Insufficient data are available to make a dosing recommendation for lopinavir/ritonavir when dosed with [HA562 trade name].
Ritonavir/ 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 [HA562 trade name] with low-dose ritonavir, the possibility of increased incidence of efavirenz-associated adverse events should be considered.
CCR-5 antagonists		
Maraviroc / efavirenz	Maraviroc AUC: ↓ Maraviroc C_{max}: Efavirenz concentrations not measured, no effect is expected.	The dose of maraviroc may need to be increased when co-administered with [HA562 trade name]; information on maraviroc should be consulted for further details since maraviroc also interacts with protease inhibitors.

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration with [HA562 trade name]
Integrase strand transfer inhibitors		
Raltegravir / efavirenz **Raltegravir** / tenofovir disoproxil	Raltegravir AUC ↓ Raltegravir AUC ↑ Tenofovir AUC ↓	No dosage adjustment is necessary if [HA562 trade name] and raltegravir are co-administered.
ANTIVIRALS AGAINST HEPATITIS B VIRUS		
Adefovir dipivoxil / tenofovir disoproxil	AUC: ↔ Cmax: ↔	[HA562 trade name] should not be administered concurrently with adefovir dipivoxil due to an expected lack of additive effect (see section 4.4).
ANTIVIRALS AGAINST HCV		
Daclatasvir / efavirenz	Daclatasvir ↓	The dose of daclatasvir should be increased to 90 mg once daily when co-administered with [HA562 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/emtricitabine/tenofovir disoproxil	Sofosbuvir ↔ Efavirenz ↔ Emtricitabine ↔ Tenofovir AUC: ↔	[HA562 trade name] and sofosbuvir can be co-administered without dose adjustment.
Sofosbuvir/velpatasvir / efavirenz/emtricitabine/tenofovir disoproxil	Sofosbuvir AUC ↔ C_{max}: ↑ Velpatasvir ↓ Efavirenz: ↔ Emtricitabine ↔ Tenofovir AUC ↑ C_{max} ↑	Co-administration of [HA562 trade name] with sofosbuvir/velpatasvir is not recommended. Co-administration of efavirenz with sofosbuvir/velpatasvir is expected to decrease the concentration of velpatasvir.
OTHER ANTIVIRALS		
Cidofovir / tenofovir disoproxil	Possible potentiation of renal toxicity	Co-administration of cidofovir and [HA562 trade name] should be avoided. If concomitant use is unavoidable, renal function should be monitored closely.

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration with [HA562 trade name]
Foscarnet / tenofovir disoproxil	Possible potentiation of renal toxicity	Co-administration of foscarnet and [HA562 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 [HA562 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 [HA562 trade name] should be avoided. If concomitant use is unavoidable, renal function should be monitored closely.
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 efavirenz should be avoided.
Fluconazole / efavirenz	No significant interaction Co-administration may potentiate the risk of QT-interval prolongation.	No dose adjustment is necessary.
ANTIBACTERIALS/ANTITUBERCULOTICS		
Aminoglycosides / tenofovir disoproxil	Possible potentiation of renal toxicity	Co-administration of an aminoglycoside and [HA562 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.

Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration with [HA562 trade name]**
Rifampicin / efavirenz	Efavirenz ↓	When co-treating, a dose increase of efavirenz should be considered in patients weighing 50 kg or more. Individual tolerability and virological response should be considered when making the dose adjustment.
Rifabutin / efavirenz	Rifabutin ↓	Increase rifabutin dose by 50% if co-treating with [HA562 trade name].
Vancomycin / tenofovir disoproxil	Possible potentiation of renal toxicity	Co-administration of vancomycin and [HA562 trade name] should be avoided. If concomitant use is unavoidable, renal function should be monitored closely.
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 [HA562 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 [HA562 trade name] should be avoided.
Lumefantrine, Halofantrine / efavirenz	These antimalarials 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 [HA562 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.

Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration with [HA562 trade name]**
Quinine / efavirenz	No formal interaction study available. Quinine is extensively metabolised by CYP3A. Co-administration with efavirenz may decrease quinine exposure and reduce its 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 [HA562 trade name].
ANTHELMINTICS		
Praziquantel / efavirenz	Praziquantel AUC ↓ Efavirenz increases hepatic metabolism of praziquantel.	Concomitant use with efavirenz is not recommended due to significant decrease in 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 [HA562 trade name] should be avoided unless plasma concentrations of carbamazepine and efavirenz can be monitored.
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 / efavirenz	No significant interaction is likely.	No dose adjustment is necessary.
Vigabatrin / efavirenz	No significant interaction is likely.	No dose adjustment is necessary.
ANTIDEPRESSANTS		
Selective Serotonin Reuptake Inhibitors (SRIs)		
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 [HA562 trade name] and citalopram or escitalopram should be avoided.
Sertraline / efavirenz	Sertraline: AUC: ↓ C_{min}, C_{max}: ↓ Efavirenz: AUC: ↔ C_{min}: ↔ (CYP3A4 induction)	When co-administered with [HA562 trade name] sertraline dose increases should be guided by clinical response.
Tricyclic antidepressants		

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration with [HA562 trade name]
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 [HA562 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 [HA562 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 [HA562 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 CYP2B6*6/*6 allele.	The combination of [HA562 trade name] and quetiapine should be avoided.
CARDIOVASCULAR MEDICINES		
Diltiazem / efavirenz	Diltiazem: AUC: ↓ Desacetyl diltiazem: AUC: ↓ N-monodesmethyl diltiazem: AUC: ↓	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.
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 [HA562 trade name] is not recommended.

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration with [HA562 trade name]
LIPID LOWERING AGENTS		
Atorvastatin / efavirenz	Atorvastatin: AUC: ↓ Total active moiety: AUC: ↓	Cholesterol levels should be periodically monitored and the dose of atorvastatin increased in case of insufficient efficacy.
Pravastatin / efavirenz	Pravastatin: AUC: ↓	Cholesterol levels should be periodically monitored and the dose of pravastatin increased in case of insufficient efficacy.
Simvastatin / 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 interaction with efavirenz is not expected.	No dose adjustment is necessary.
HORMONAL CONTRACEPTIVES AND HORMONE REPLACEMENT THERAPY		
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.
Depot medroxyprogesterone acetate / efavirenz	The pharmacokinetics of depot medroxyprogesterone acetate 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 [HA562 trade name], depot medroxyprogesterone acetate may be injected every 8–10 weeks instead of every 12 weeks.
Etonogestrel / efavirenz	Etonogestrel exposure may be decreased due to the CYP3A induction of efavirenz. There have been reports of contraceptive failure with etonogestrel in efavirenz-exposed patients.	A reliable alternative method of contraception should be considered.

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration with [HA562 trade name]
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.
Drospirenone HRT, dydrogesterone HRT, estradiol, levonogestrel HRT / efavirenz		Co-administration may decrease comedication exposure. Monitor for signs of hormone deficiency.
IMMUNOSUPPRESSANTS		
Ciclosporin **Sirolimus** **Tacrolimus** / efavirenz	Interaction not formally studied. Decreased exposure of these immunosuppressants may be expected when co-treating with 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 [HA562 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 [HA562 trade name] should be avoided. If concomitant use is unavoidable, renal function should be monitored closely.
Cisplatin / emtricitabine	Cisplatin is eliminated renally via OCT2 and MATE1. Cisplatin and emtricitabine could potentially compete for MATE1 which could slow their elimination.	Potential renal toxicity. Monitor renal function closely.
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		
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.

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration with [HA562 trade name]
Pentamidine / tenofovir disoproxil	Possible potentiation of renal toxicity	Co-administration of pentamidine and [HA562 trade name] should be avoided. If concomitant use is unavoidable, renal function should be monitored closely.
Methadone / efavirenz	Methadone AUC ↓ Co-administration may potentiate the risk of QT-interval prolongation.	Monitor for withdrawal symptoms and increase methadone dose if necessary. Monitor ECG for QT prolongation; risk is increased with higher methadone doses.
Buprenorphine / efavirenz	Buprenorphine AUC ↓ norbuprenorphine AUC ↓ (active metabolite)	Monitor for withdrawal symptoms and increase buprenorphine dose if necessary.
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.
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: ↑	No dose adjustment necessary.
Ginkgo biloba extracts / efavirenz	Efavirenz ↓	Concomitant treatment is not recommended.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

The use of [HA562 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. A large amount of data on pregnant women (more than 1000 pregnancy outcomes) indicates no malformations or fetal/neonatal toxicity associated with emtricitabine and tenofovir disoproxil.

Animal studies on emtricitabine and tenofovir disoproxil do not indicate reproductive toxicity (see section 5.3). Studies of efavirenz in animals have shown reproductive toxicity (see section 5.3).

Breast-feeding

Efavirenz, emtricitabine 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 human data on the effect of [HA562 trade name] are available. Animal studies do not indicate harmful effects of efavirenz, emtricitabine 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, 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 or operating machinery.

4.8 Undesirable effects

Summary of the safety profile

Adverse reactions of the combination of efavirenz, emtricitabine and tenofovir disoproxil are generally consistent with those of the individual components. The most frequent 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%). Anorexia is also a common adverse reaction associated with the combination.

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 [HA562 trade name] (see section 4.4).

Discontinuation of [HA562 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 [HA562 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 reactions considered at least possibly related to treatment with the components of [HA562 trade name] from clinical trial and post-marketing experience are listed below by body system organ class and 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).

Blood and lymphatic system disorders

Common	neutropenia
Uncommon	anaemia

Immune system disorders

Common	hypersensitivity

Metabolism and nutrition disorders

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

Psychiatric disorders

Common	abnormal dreams, anxiety, depression, insomnia

Uncommon	emotional lability, aggression, confusional state, euphoric mood, hallucination, mania, paranoia, psychosis, suicide attempt, suicide ideation, catatonia
Rare	delusion, neurosis, completed suicide

Nervous system disorders

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

Gastrointestinal disorders

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

Hepatobiliary disorders

Common	elevations of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and/or gamma-glutamyl transferase (GGT), hyperbilirubinaemia
Uncommon	hepatitis
Rare	hepatic failure, hepatic steatosis

Skin and subcutaneous tissue disorders

Very common	rash
Common	pruritus, skin discolouration, urticaria
Uncommon	angioedema, erythema multiforme, Stevens-Johnson syndrome
Rare	photoallergic dermatitis

Musculoskeletal and connective tissue disorders

Very common	elevated creatine kinase
Common	decreased bone mineral density
Uncommon	rhabdomyolysis, muscular weakness
Rare	myopathy, osteomalacia

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

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, pain

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 therapy with efavirenz. In most patients, rash resolved with continuing therapy with efavirenz within a month. [HA562 trade name] can be restarted in patients interrupting therapy because of rash. Use of an antihistamine or a corticosteroid, or both, is recommended when restarting [HA562 trade name].

Psychiatric symptoms

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

Nervous system symptoms

Nervous system symptoms are common with efavirenz. 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 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 [HA562 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 sections 4.2 and 4.4).

Renal impairment

As [HA562 trade name] may cause renal damage, monitoring of renal function is recommended (see sections 4.4). Proximal renal tubulopathy generally resolved or improved after discontinuing tenofovir disoproxil. However, in some patients, decline in creatinine clearance did not completely resolve despite discontinuing tenofovir disoproxil.

Patients with risk factors for 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 [HA562 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, was 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 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) 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 risk factors, advanced HIV disease or long-term combined antiretroviral therapy. The frequency of this is unknown.

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. The effect of tenofovir disoproxil on bone mass in those not fully grown is a specific theoretical safety concern.

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 in patients infected with HIV without co-infection. However, as expected, AST and ALT levels were raised 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).

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 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 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 has antiviral activity against most non-clade B isolates (subtypes A, AE, AG, C, D, F, G, J, and N) but it has reduced antiviral activity against group O viruses. Emtricitabine has antiviral activity against HIV-1 clades A, B, C, D, E, F, and G. Tenofovir has 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

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.

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).

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.

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, where 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 hepatitis B virus

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

5.2 Pharmacokinetic properties

Absorption of [HA562 trade name]

The absorption characteristics of [HA562 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)**		
	Efavirenz	**Emtricitabine**	**Tenofovir**
Maximum concentration (C_{max})	2401 ± 743 ng/mL	2191 ± 527 ng/mL	289 ± 73 ng/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	56539 ± 18060 ng·h/mL*	10895 ± 2094 ng·h/mL	2463 ± 563 ng·h/mL
Time to attain maximum concentration (t_{max})	3.43 ± 1.26 h	1.80 ± 0.85 h	1.47 ± 0.74 h

* 0-72h

Pharmacokinetics of efavirenz, emtricitabine and tenofovir disoproxil

	Efavirenz	**Emtricitabine**	**Tenofovir disoproxil**
General	Peak efavirenz plasma concentrations are attained by 5 hours following single oral administration.	Emtricitabine is rapidly and extensively absorbed following oral administration with peak plasma concentrations occurring at 1 to 2 hours post-dose.	Tenofovir disoproxil is a water-soluble ester prodrug, which is rapidly converted in vivo to tenofovir. Tenofovir is converted intracellularly to tenofovir monophosphate and to the active component, tenofovir diphosphate.
Absorption			

<table>
<tr><th></th><th>Efavirenz</th><th>Emtricitabine</th><th>Tenofovir disoproxil</th></tr>
<tr><td>Absolute bioavailability</td><td>Not available</td><td>75–93%</td><td>Not available</td></tr>
<tr><td>Oral bioavailability</td><td>40–45%</td><td>Not available</td><td>25% in fasted patients</td></tr>
<tr><td>Food effect</td><td><table><tr><th></th><th>AUC(0-∞)</th><th>Cmax</th></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><th>AUC(0-∞)</th><th>Cmax</th><th>Tmax</th></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>Not available</td><td>After IV admin
1.4 ± 0.3 L/kg</td><td>800 mL/kg</td></tr>
<tr><td>Plasma protein binding in vitro</td><td>> 99% (predominantly to albumin)</td><td>< 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>
<tr><td colspan="4">Elimination</td></tr>
<tr><td>Elimination half-life</td><td>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.</td><td>Approximately 10 h
Emtricitabine triphosphate: 39 h in intracellular peripheral blood mononuclear cells.</td><td>12–18 h.
Tenofovir diphosphate: 10 h in intracellular activated resting peripheral blood mononuclear cells and 50 h in resting peripheral blood mononuclear cells.</td></tr>
</table>

	Efavirenz	**Emtricitabine**	**Tenofovir disoproxil**
Mean systemic clearance (Cl/F)	Not available	Averaged 307 mL/minute (4.03 mL/minute/kg).	230 mL/h/kg
% of dose excreted in urine	14–34% recovered in urine and < 1% excreted unchanged	Approx. 86% recovered in urine (13% recovered in urine as three metabolites)	70-80% as unchanged drug
% of dose excreted in faeces	Not available	Approx. 14%	Not available
Pharmaco-kinetic 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 daily).	Linear pharmacokinetics (dose range 25 to 200 mg)	Linear pharmacokinetics (dose range 75 to 600 mg)
Drug interactions *(in vitro*)			
Transporters	Not available	Not available	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. It inhibits CYP3A4 in vitro.	No inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. No inhibition of uridine-5'-diphosphoglucuronyl transferase.	No significant inhibition of CYP3A4, CYP2D6, CYP2C9, CYP2E1, or CYP1A1/2.

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 similar 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 but they do not appear to be less tolerant of 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 higher than 80 mL/minute; mild impairment with creatinine clearance of 50–79 mL/minute; moderate impairment with creatinine clearance of 30–49 mL/minute and severe impairment with creatinine clearance of 10–29 mL/minute).

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 2.2 µg·h/mL (12%) in patients with normal renal function, to 3.1 µg·h/mL (30%), 6.0 µg·h/mL (42%) and 16.0 µg·h/mL (45%) in patients with mild, moderate and severe renal impairment, respectively.

In patients with end-stage renal disease requiring haemodialysis, between-dialysis drug exposures substantially increased over 72 hours to 53 µg·h/mL (19%) of emtricitabine, and over 48 hours to 42.9 µg·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.

[HA562 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 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. [HA562 trade name] should be administered with caution to patients with mild hepatic impairment (see sections 4.3 and 4.4).

[HA562 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 pharmacokinetics of emtricitabine have not been studied in patients with varying degrees of hepatic insufficiency who are not infected with hepatitis B virus. In general, emtricitabine pharmacokinetics in patients infected with hepatitis B 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. 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, genotoxicity, carcinogenic potential, and toxicity to reproduction and development.

Tenofovir

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

Studies in rats, dogs and monkeys revealed kidney and bone toxicity, 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 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 revealed positive results in the in vitro mouse lymphoma assay, equivocal results in one of the strains used in the Ames test, and weakly positive results in a urine drug test (UDS) in primary rat hepatocytes. However, it was negative in an in vivo mouse bone marrow micronucleus assay.

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

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: Microcrystalline cellulose
Croscarmellose sodium
Hydroxypropyl cellulose
Sodium lauryl sulfate
Pregelatinized starch
Magnesium stearate

Film coat: Polyvinyl alcohol (partly hydrolysed)
Titanium dioxide
Polyethylene glycol
Talc
Red iron oxide
Black iron oxide

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

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C, in dry place protected from light.

6.5 Nature and contents of container

HDPE container

[HA562 trade name] is provided a round, white HDPE bottle containing 30 tablets. The bottle has (120cc, 38-400 neck finish) with child-resistant polypropylene closure or continuous thread closure, with 3g silica gel sachet (2x3g).

[HA562 trade name] is provided a round, white HDPE bottle containing 90 tablets. The bottle has (250cc, 53-400 neck finish) with child-resistant polypropylene closure or continuous thread closure, with 3g silica gel sachet (2× 3g).

[HA562 trade name] is provided a round, white HDPE bottle containing 180 tablets. The bottle has (500cc, 53-400 neck finish) with child-resistant polypropylene closure or continuous thread closure, with 3g silica gel sachet (3×3g).

6.6 Special precautions for disposal and other handling

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

7. SUPPLIER

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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

HA562

9. DATE OF PREQUALIFICATION

17 November 2014

10. DATE OF REVISION OF THE TEXT

May 2026

References

General reference sources for this SmPC include:

Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. Geneva: World Health Organization; 2021, available at https://www.who.int/publications/i/item/9789240031593

Efavirenz/Emtricitabine/Tenofovir disoproxil Mylan 600 mg/200 mg/245 mg film-coated tablets: summary of product characteristics. European Medicines Agency; 18 November 2025, available at: https://www.ema.europa.eu/en/documents/product-information/efavirenz-emtricitabine-tenofovir-disoproxil-mylan-epar-product-information_en.pdf

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

Truvada 200 mg/245 mg film-coated tablets: summary of product characteristics. European Medicines Agency, 29 February 2024, available at: https://www.ema.europa.eu/en/documents/product-information/truvada-epar-product-information_en.pdf

Emtriva 200 mg hard capsules: summary of product characteristics. European Medicines Agency, 18 April 2023, available at: https://www.ema.europa.eu/en/documents/product-information/emtriva-epar-product-information_en.pdf

Viread 245 mg film-coated tablets: summary of product characteristics. European Medicines Agency, 29 February 2024, available at: https://www.ema.europa.eu/en/documents/product-information/viread-epar-product-information_en.pdf

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 specific sections of the SmPC include:

Section 4.5

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

Sections 4.6 and 5.3

British HIV Association. British HIV association guidelines for the management of HIV in pregnancy and postpartum 2018 (2020 third interim update). 2020. Available at: https://www.bhiva.org/file/5f1aab1ab9aba/BHIVA-Pregnancy-guidelines-2020-3rd-interim-update.pdf

Efavirenz: Drug and Lactation Database (LactMed), available at: https://www.ncbi.nlm.nih.gov/books/NBK501534/pdf/Bookshelf_NBK501534.pdf

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

Emtricitabine: Drugs and Lactation Database. National Library of Medicine; 15 July 2025 (https://www.ncbi.nlm.nih.gov/books/NBK501548)

All references last accessed in March 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