SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT
Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets*

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
Blue coloured, capsule shaped, biconvex film-coated tablets engraved TEE on one side and plain on other side.

No score line. Tablets should not be divided.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets is a fixed dose combination of tenofovir disoproxil, emtricitabine and efavirenz. It is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and adolescents (from 10 years of age and weighing at least 35 kg).

Consideration should be given to official treatment guidelines for HIV-1 infection, e.g. by WHO: [http://www.who.int/hiv/pub/arv/arv-2016/en/](http://www.who.int/hiv/pub/arv/arv-2016/en/).

4.2 Posology and method of administration
Therapy should be prescribed by a physician experienced in the management of HIV-1 infection.

Adults and adolescents
The recommended dose of Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets is one tablet taken orally once daily.

Special populations

Children:
Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets is not recommended for use in children below 10 years of age due to a lack of data on safety and efficacy.

Elderly:
Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets should be administered with caution to elderly patients (see section 4.4).

* Trade names are not prequalified by WHO. This is the national medicines regulatory agency’s (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.
Dose adjustments
Where discontinuation of therapy with one of the components of Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets is indicated or where dose modification is necessary, separate preparations of efavirenz, emtricitabine and tenofovir disoproxil fumarate are available. Please refer to the Summary of Product Characteristics for these medicinal products.

If Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets is co-administered with rifampicin in patients weighing 50 kg or more, an additional 200 mg/day (800 mg total) of efavirenz may be considered (see section 4.4 and 4.5).

Renal impairment
Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets is not recommended for patients with moderate or severe renal impairment (creatinine clearance (CrCl) < 50 ml/min). Patients with moderate or severe renal impairment require dose interval adjustment of emtricitabine and tenofovir disoproxil fumarate that cannot be achieved with the combination tablet (see sections 4.4 and 5.2).

Hepatic impairment:
The pharmacokinetics of Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets have not been studied in patients with hepatic impairment. Patients should be monitored carefully for adverse reactions, especially nervous system symptoms related to efavirenz (see sections 4.3 and 4.4).

If Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets is discontinued in patients co-infected with HIV and HBV, these patients should be closely monitored for evidence of exacerbation of hepatitis (see section 4.4).

If therapy with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets 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. Because of interpatient variability in these parameters and concerns regarding development of resistance, HIV treatment guidelines should be consulted, also taking into consideration the reason for discontinuation.

Method of administration
It is recommended that Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets be swallowed whole with water.

It is recommended that Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets be taken on an empty stomach since food may increase efavirenz exposure and may lead to an increase in the frequency of adverse reactions (see sections 4.4 and 4.8).

In order to improve the tolerability of efavirenz with respect to undesirable effects on the nervous system, bedtime dosing is recommended (see section 4.8)

It is anticipated that tenofovir exposure will be approximately 30% lower following administration of Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets on an empty stomach as compared to the individual component tenofovir disoproxil fumarate when taken with food (see section 5.2). In virologically suppressed patients, the clinical relevance of this reduction can be expected to be limited (see section 5.1).
4.3 Contraindications

Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets is contraindicated in patients with clinically significant hypersensitivity to tenofovir, emtricitabine, efavirenz or to any of the excipients contained in the formulation.

Use of other drugs metabolized through cytochrome P450 (CYP) 3A4 could result in inhibition of metabolism of efavirenz and create the potential for serious and/or life-threatening adverse reactions (for example, cardiac arrhythmias, prolonged sedation or respiratory depression) (see section 4.5). Therefore, Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets must not be co-administered with terfenadine, astemizole, cisapride, midazolam, triazolam, pimozide, bepridil, or ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine).

Herbal preparations containing St.John’s wort (Hypericum perforatum) must not be used while taking Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets due to the risk of decreased plasma concentrations and reduced clinical effects of efavirenz (see section 4.5).

Efavirenz significantly decreases voriconazole plasma concentrations while voriconazole also significantly increases efavirenz plasma concentrations. Since Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets is a fixed-dose combination product, the dose of efavirenz cannot be altered; therefore, voriconazole and Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets must not be co-administered (see section 4.5).

4.4 Special warnings and precautions for use

General

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

Co-administration with other medicinal products

As a fixed combination, Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets should not be administered concomitantly with other medicinal products containing any of the same active components, emtricitabine or tenofovir disoproxil.

Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets should not be co-administered with products containing efavirenz unless needed for dose adjustment e.g. with rifampicin (see section 4.2).

Due to similarities with emtricitabine, Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets should not be administered concomitantly with other cytidine analogues, such as lamivudine (see section 4.5).

Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets should not be administered concomitantly with medicinal products containing adefovir dipivoxil or tenofovir alafenamide.

No data are available on the safety and efficacy of Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets in combination with other antiretroviral agents.

Co-administration of Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets and didanosine is not recommended since exposure to didanosine is significantly increased following co-administration with tenofovir disoproxil (see section 4.5). Rarely, pancreatitis and lactic acidosis, sometimes fatal have been reported.

Concomitant use of Ginkgo biloba extracts with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets is not recommended (see section 4.5).

Co-administration with amodiaquine is not recommended since amodiaquine exposure significantly increased following co-administration with efavirenz. Hepatotoxicity has been observed (see section 4.5).
Antivirals against HCV
Co-administration with boceprevir is not recommended, since plasma concentrations of simeprevir significantly decreased due to CYP3A induction by efavirenz, which may result in loss of therapeutic effect of simeprevir (see section 4.5).

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

Co administration of ledipasvir/sofosbuvir and efavirenz/emtricitabine/tenofovir disoproxil resulted in increased exposure to tenofovir and moderate reductions in ledipasvir exposure. Tenofovir-associated adverse reactions should be monitored in patients receiving ledipasvir/sofosbuvir and Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets (see section 4.5).

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

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

Opportunistic infections
Patients receiving Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by healthcare providers experienced in the treatment of patients with HIV associated diseases.

Transmission of HIV
While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Liver disease
The pharmacokinetics, safety and efficacy of efavirenz/emtricitabine/tenofovir disoproxil 600mg/200mg/245mg tablets have not been established in patients with significant underlying liver disorders (see section 5.2). Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets is contraindicated in patients with severe hepatic impairment (see section 4.3) and not recommended in patients with moderate hepatic impairment. Since efavirenz is principally metabolised by the CYP system, caution should be exercised in administering Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets to patients with mild hepatic impairment. These patients should be carefully monitored for efavirenz adverse reactions, especially nervous system symptoms. Laboratory tests should be performed to evaluate their liver disease at periodic intervals (see section 4.2).

Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy (CART) and should be monitored according to standard practice. If there is evidence of worsening liver disease or persistent elevations of serum transaminases to greater than 5 times the upper limit of the normal range, the benefit of continued therapy with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets needs to be weighed against the potential risks of significant liver toxicity. In such patients, interruption or discontinuation of treatment must be considered (see section 4.8).
In patients treated with other medicinal products associated with liver toxicity, monitoring of liver enzymes is also recommended.

**Liver toxicity**

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

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

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

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

In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant Summary of Product Characteristics for these medicinal products.

The safety and efficacy of emtricitabine and tenofovir disoproxil have not been established for the treatment of chronic HBV infection. Emtricitabine and tenofovir individually and in combination have shown activity against HBV (see section 5.1). Limited clinical experience suggests that emtricitabine and tenofovir disoproxil have anti-HBV activity when used in antiretroviral combination therapy to control HIV infection. Discontinuation of Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets 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 it should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

**Psychiatric symptoms**

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

**Nervous system symptoms**

Symptoms including, but not limited to, dizziness, insomnia, somnolence, impaired concentration and abnormal dreaming are frequently reported undesirable effects in patients receiving efavirenz in clinical studies. Dizziness was also seen in clinical studies with emtricitabine and tenofovir disoproxil. Headache has been reported in clinical studies with emtricitabine (see section 4.8). Nervous system symptoms associated with efavirenz usually begin during the first one or two days of therapy and generally resolve after the first two to four weeks. Patients should be informed that if they do occur, these common symptoms are likely to improve with continued therapy and are not predictive of subsequent onset of any of the less frequent psychiatric symptoms.

Convulsions have been observed in patients receiving efavirenz, generally in the presence of a known medical history of seizures. Patients who are receiving concomitant anticonvulsant medicinal products primarily metabolised by the liver, such as phenytoin, carbamazepine and phenobarbital, may require periodic monitoring of plasma levels. In a drug interaction study, carbamazepine plasma concentrations were decreased when carbamazepine was co-administered with efavirenz (see section 4.5). Caution must be taken in any patient with a history of seizures.
Renal function
Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets is not recommended for patients with moderate or severe renal impairment (creatinine clearance < 50 ml/min) or in patients requiring haemodialysis. Patients with moderate or severe renal impairment require a dose adjustment of emtricitabine and tenofovir disoproxil that cannot be achieved with this combination tablet (see sections 4.2 and 5.2).
Renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir disoproxil in clinical practice (see section 4.8).
Use of Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets should be avoided with concurrent or recent use of a nephrotoxic medicinal product. If concomitant use of Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets and nephrotoxic agents (e.g. aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir, interleukin-2) is unavoidable, renal function must be monitored weekly (see section 4.5).
Cases of acute renal failure after initiation of high dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs) have been reported in patients treated with tenofovir disoproxil and with risk factors for renal dysfunction. If Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets is co-administered with an NSAID, renal function should be monitored adequately.

If the creatinine test is routinely available, use the estimated glomerular filtration rate at baseline before initiating tenofovir disoproxil-containing regimens.
Benefits and risks should be carefully weighed when initiating therapy with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets in patients at increased risk for renal toxicity, i.e. patients more than 50 years of age, with low body weight (<50 kg), diabetes, uncontrolled hypertension, renal failure, or concomitant use of of boosted PIs or nephrotoxic drugs (see section 4.2).
Creatinine testing during therapy is particularly advisable for high-risk patients to detect and limit further progression of renal impairment. If available, also serum phosphate should be measured in these patients. If serum phosphate is < 1.5 mg/dl (0.48 mmol/l) or creatinine clearance is decreased to < 50 ml/min in any patient receiving emtricitabine and tenofovir disoproxil, renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations (see section 4.8, proximal tubulopathy).
Consideration should also be given to interrupting treatment with tenofovir disoproxil in patients with creatinine clearance decreased to < 50 ml/min or decreases in serum phosphate below 1.0 mg/dl (0.32 mmol/l). Interrupting treatment with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets should also be considered in case of progressive decline of renal function when no other cause has been identified. Where discontinuation of therapy with one of the components of Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets is indicated or where dose modification is necessary, separate preparations of efavirenz, emtricitabine and tenofovir disoproxil are available.

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

In HIV-1 infected adolescents 12 years of age and older, the mean rate of bone gain was less in the tenofovir disoproxil-treated group compared to the placebo group. Skeletal growth (height) appeared to be unaffected. Markers of bone turnover in tenofovir disoproxil-treated adolescents suggest increased bone turnover, consistent with the effects observed in adults. Due to the possible effects of tenofovir on bone metabolism,
Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets should only be used in adolescents under the age of 18 if the benefits are considered to exceed the risk (see also section 4.8).

Bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy (see section 4.8). If bone abnormalities are suspected then appropriate consultation should be obtained.

**Osteonecrosis**

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

**Rash**

A mild-to-moderate rash very commonly develops within two weeks after starting efavirenz and does not require treatment discontinuation. The rash usually resolves within two weeks. Appropriate antihistamines and/or corticosteroids may improve tolerability and hasten the resolution of rash. Severe rash or erythema, including Stevens-Johnson syndrome, requires immediate discontinuation (see section 4.8).

Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets is not recommended for patients who have had a life-threatening cutaneous reaction (e.g., Stevens-Johnson syndrome) while taking an NNRTI.

**Weight and metabolic parameters**

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

**Mitochondrial dysfunction following exposure in utero**

Nucleos(t)ide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV negative infants exposed in utero and/or postnatally to nucleoside analogues; these have predominantly concerned treatment with regimens containing zidovudine. The main adverse reactions reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactataemia, hyperlipasaemia). These events have often been transitory. Late onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently unknown. These findings should be considered for any child exposed in utero to nucleos(t)ide analogues, who present with severe clinical findings of unknown etiology, particularly neurologic findings. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

**Immune Reactivation Syndrome**

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

Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.
Effect of food
The administration of Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets with food may increase efavirenz exposure (see section 5.2) and may lead to an increase in frequency of adverse reactions (see section 4.8). It is recommended that Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets be taken on an empty stomach, preferably at bedtime.

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

Excipients
Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption may experience symptoms of intolerance when using it.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions relevant to efavirenz
As Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets contains efavirenz, emtricitabine and tenofovir disoproxil, any interactions that have been identified with these agents individually may occur with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets. Interaction studies with these agents have only been performed in adults.

As a fixed combination, Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets should not be administered concomitantly with other medicinal products containing the components, emtricitabine or tenofovir disoproxil. Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets should not be co-administered with products containing efavirenz unless needed for dose adjustment e.g. with rifampicin (see section 4.2). Due to similarities with emtricitabine, Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets should not be administered concomitantly with other cytidine analogues, such as lamivudine.

Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets should not be administered concomitantly with adefovir dipivoxil or with medicinal products containing tenofovir alafenamide.

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

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

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

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

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

Interactions relevant to emtricitabine:

In vitro, emtricitabine did not inhibit metabolism mediated by any of the following human CYP450 isoforms: 1A2, 2A6, 2B6, 2C9, 2C19, 2D6 and 3A4, and did not inhibit enzymatic glucuronidation.
There are no clinically significant interactions when emtricitabine is co-administered with indinavir, zidovudine, stavudine or famciclovir. Emtricitabine is primarily excreted via glomerular filtration and active tubular secretion. With the exception of famciclovir and tenofovir disoproxil, the effect of co-administration of emtricitabine with medicinal products that are excreted by the renal route, or other medicinal products known to affect renal function, has not been evaluated. Co-administration of Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets with medicinal products that are eliminated by active tubular secretion may lead to an increase in serum concentrations of either emtricitabine or a co-administered medicinal product due to competition for this elimination pathway. There is no clinical experience or virologic rationale for the co-administration of emtricitabine and cytidine analogues. Consequently, Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets should not be administered in combination with lamivudine for the treatment of HIV infection (see section 4.4).

Interactions relevant to tenofovir

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

Renally eliminated medicinal products

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

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

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

Table of drug interactions for Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets

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

**Interaction**

**Recommendations concerning co-administration with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets**

- mg/300 mg Tablets should not be co-administered, as the additive effect of abacavir is expected to be limited or absent.

**Lamivudine / emtricitabine**

- Lamivudine and Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets should not be co-administered, due to the similarity between emtricitabine and lamivudine, and consequently expected lack of additive effects (see section 4.4.).

**Didanosine(400 mg q.d.) / tenofovir disoproxil**

- Didanosine AUC↑ 40-60%

  - The risk of didanosine-related adverse effects appears to be increased, and CD4 cells may decrease significantly on co-administration.

  - Didanosine at 250 mg co-administered with tenofovir within several different antiretroviral combination regimens has been associated with a high rate of virological failure. Co-administration of Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets and didanosine is not recommended (see section 4.4.).

**Non-nucleoside inhibitors of reverse transcriptase**

- **Nevirapine**

  - Concomitant use not recommended because of additive toxicity and no benefit in terms of efficacy.

- **Etravirine**

  - Interaction not studied. For co-administration of efavirenz with low-dose ritonavir in combination with a protease inhibitor, see section on ritonavir above.

### Protease inhibitors

- **Fosamprenavir/ritonavir(700/100 mg b.i.d)) / efavirenz**

  - No clinically significant pharmacokinetic interaction

  - No dose adjustment necessary.

- **Saquinavir /ritonavir / efavirenz**

  - Insufficient data are available for making a dosing recommendation for saquinavir, with or without ritonavir, when co-administered with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets. Co-administration with saquinavir, with or without ritonavir, is not recommended.

- **Indinavir / efavirenz**

  - Insufficient data are available to make a dosing recommendation for
### Medicinal products by therapeutic areas

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Recommendations concerning co-administration with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets</th>
</tr>
</thead>
</table>
| **Indinavir/ritonavir (800/100 mg b.i.d.) / efavirenz** | Indinavir AUCss ↓ 25%, Cτrough ↓ 50%  
Concomitant use with boosted indinavir is only recommended when it is possible to monitor the plasma concentration of indinavir. |
| **Ritonavir (500 mg b.i.d) / efavirenz** | Interaction studies have shown moderate increases in the AUC for both ritonavir and efavirenz.  
Avoid concomitant use with full-dose ritonavir, due to low tolerability. When using Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets with low-dose ritonavir, the possibility of an increase in the incidence of efavirenz-associated adverse events should be considered, due to possible pharmacodynamic interaction. |
| **Lopinavir/ritonavir soft capsules or oral solution / efavirenz** | Substantial decrease in lopinavir exposure, necessitating dosage adjustment of lopinavir/ritonavir. When used in combination with efavirenz and two NRTIs, 533/133 mg lopinavir/ritonavir (soft capsules) twice daily yielded similar lopinavir plasma concentrations as compared to lopinavir/ritonavir (soft capsules) 400/100 mg twice daily without efavirenz (historical data).  
Insufficient data are available to make a dosing recommendation for lopinavir/ritonavir when dosed with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets. Co-administration of lopinavir/ritonavir and Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets is not recommended. |

Lopinavir Cmin ↓≈ 40%
## Medicinal products by therapeutic areas

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Recommendations concerning co-administration with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets</th>
</tr>
</thead>
</table>
| **Lopinavir/ritonavir tablets**  
(400/100 mg b.i.d.)  
/efavirenz  
(500/125 mg b.i.d.)  
/efavirenz  
Lopinavir/ritonavir (400 mg/100 mg b.i.d.)  
/tenofovir disoproxil | Lopinavir concentrations: similar to lopinavir/ritonavir 400/100 mg twice daily without efavirenz  
Lopinavir/ritonavir: No significant effect on lopinavir/ritonavir PK parameters.  
Tenofovir:  
AUC: ↑ 32%  
Cmax: ↔  
Cmin: ↑ 51% | Concomitant use of Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets and unboosted atazanavir is not recommended. |
| **Atazanavir** 400mg / efavirenz  
Atazanavir (400 mg q.d.)/ tenofovir disoproxil | Atazanavir AUCss ↓ 74%,  
Cmin ↓ 93%  
Atazanavir:  
AUC: ↓ 25%  
Cmax: ↓ 21%  
Cmin: ↓ 40%  
Tenofovir:  
AUC: ↑ 24%  
Cmax: ↑ 14%  
Cmin: ↑ 22% | |
<table>
<thead>
<tr>
<th>Medicinal products by therapeutic areas</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets</th>
</tr>
</thead>
</table>
| **Atazanavir/ritonavir / tenofovir disoproxil (300 mg q.d./100 mg q.d./245 mg q.d.)** | Atazanavir:  
AUC: ↓ 25% (↓ 42 to ↓ 3)  
C<sub>max</sub>: ↓ 28% (↓ 50 to ↑ 5)  
C<sub>min</sub>: ↓ 26% (↓ 46 to ↑ 10)  
Co-administration of atazanavir/ritonavir with tenofovir disoproxil resulted in increased exposure to tenofovir. Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders. | Co-administration of atazanavir/ritonavir and Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets is not recommended. |
| **Atazanavir/ritonavir / efavirenz (400 mg q.d./100 mg q.d./600 mg q.d., all administered with food)** | Atazanavir:  
AUC: ↔* (↓ 9% to ↑ 10%)  
C<sub>max</sub>: ↑ 17%* (↑ 8 to ↑ 27)  
C<sub>min</sub>: ↓ 42%* (↓ 31 to ↓ 51)  
Atazanavir:  
AUC: ↔**/* (↓ 10% to ↑ 26%)  
C<sub>max</sub>: ↑ 12%** (↑ 5 to ↑ 26%)  
C<sub>min</sub>: ↓ 12%** (↓ 16 to ↑ 49)  
(CYP3A4 induction).  
* When compared to atazanavir 300 mg/ritonavir 100 mg q.d. in the evening without efavirenz. This decrease in atazanavir C<sub>min</sub> might negatively impact the efficacy of atazanavir.  
** based on historical comparison. | The combination of Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets and tipranavir/ritonavir should be avoided. |
| **Atazanavir/ritonavir / efavirenz (400 mg q.d./200 mg q.d./600 mg q.d., all administered with food)** | Appropriate data on the interaction between the approved tipranavir regimen and efavirenz are lacking. | The combination of Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets and tipranavir/ritonavir should be avoided. |
| **Tipranavir/ritonavir / efavirenz** | | |
| **Darunavir/ritonavir (300/100 mg b.i.d) / efavirenz (600 mg q.d)** | Darunavir  
AUC ↓ 13%,  
C<sub>min</sub> ↓ 31%.  
Efavirenz  
AUC ↑ 21%,  
C<sub>min</sub> ↑ 17% | Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets in combination with darunavir/ritonavir 800/100mg once daily may result in suboptimal darunavir C<sub>min</sub>.  
If Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets is to be used in combination with darunavir/ritonavir, the darunavir/ritonavir 600/100mg twice daily regimen should be used. Darunavir/ritonavir should be used with caution in combination |
### Medicinal products by therapeutic areas

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Recommendations concerning co-administration with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Darunavir/ritonavir (300 mg/100 mg b.i.d.) / tenofovir disoproxil</strong></td>
<td>Monitoring of renal function may be indicated, particularly in patients with underlying systemic or renal disease, or in patients taking nephrotoxic agents.</td>
</tr>
<tr>
<td>Darunavir: No significant effect on darunavir/ritonavir PK parameters.</td>
<td></td>
</tr>
</tbody>
</table>
| Tenofovir: AUC: ↑ 22%  
C<sub>min</sub>: ↑ 37% |  |
| **Darunavir/ritonavir/emtricitabine** | Interaction not studied. No interaction expected. |
| **CCR-5 antagonists** |  |
| Maraviroc (100 mg b.i.d) / efavirenz 600 mg q.d | Maraviroc AUC: ↓ 45%  
Maraviroc C<sub>max</sub>: ↓ 51% |
| Efavirenz concentrations not measured, no effect is expected. |  |
| **Integrase strand transfer inhibitors** |  |
| Raltegravir (400 mg single dose) / efavirenz | Raltegravir AUC ↓ 36%  
Raltegravir AUC ↑ 49%  
Raltegravir C<sub>max</sub> ↑ 64% |
| No dosage adjustment is necessary if Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets and raltegravir are co-administered. |  |
| **ANTIVIRALS AGAINST HBV** |  |
| Adefovir dipivoxil / tenofovir disoproxil | AUC: ↔  
C<sub>max</sub>: ↔ |
| Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets should not be administered concurrently with adefovir dipivoxil due to an expected lack of additive effect (see section 4.4). |  |
| **ANTIVIRALS AGAINST HCV** |  |
| Boceprevir / efavirenz (800 mg t.i.d/600 mg q.d.) | Boceprevir  
AUC: ↔19%*  
C<sub>max</sub>: ↔8%  
C<sub>min</sub>: ↓44% |
| Plasma trough concentrations of boceprevir were decreased when administered with efavirenz. The clinical outcome of this observed reduction of boceprevir trough |  |
### Medicinal products by therapeutic areas

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Recommendations concerning co-administration with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td>Efavirenz AUC: ↔20% Cmax: ↔11% Concentrations have not been directly assessed. Co-administration should be avoided (see section 4.4).</td>
</tr>
</tbody>
</table>

**Boceprevir / emtricitabine**

- No interaction expected

**Boceprevir (800 mg t.i.d) / tenofovir disoproxil**

- No interaction observed

**Daclatasvir (60mg or 120 mg q.d.) / efavirenz**

- Daclatasvir
  - AUC*: ↓32%
  - Cmax*: ↓17%
  - Cmin*: ↓59%
  - Induction of CYP3A4 by efavirenz
  - *Results are dose-normalised to 60 mg dose.

- The dose of daclatasvir should be increased to 90 mg once daily when coadministered with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets

**Daclatasvir (60mg) / emtricitabine**

- No interaction expected

**Daclatasvir (60mg) / tenofovir disoproxil**

- No interaction observed

**Dasabuvir**

- See Ombitasvir/Paritaprevir/ritonavir below

- Concomitant use with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets is contraindicated (see section 4.3).

**Elbasvir/grazoprevir (50mg/200mg q.d.)/efavirenz**

- Elbasvir
  - AUC ↓54%
  - Cmax ↓45%
  - C24 ↓59%

- Grazoprevir
  - AUC ↓83%
  - Cmax ↓87%
  - C24 ↓69%

- Efavirenz
  - AUC ↔
  - Cmax ↔
  - C24 ↔

- Concomitant use with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets is contraindicated (see section 4.3).

**Elbasvir/grazoprevir (50mg/200mg q.d.)/emtricitabine**

- No interaction observed

**Elbasvir/grazoprevir (50mg/200mg q.d.)/tenofovir disoproxil**

- No interaction observed

**Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + efavirenz/emtricitabine/tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)**

- Ledipasvir
  - AUC: ↓34%
  - Cmax: ↓34%
  - Cmin: ↓34%

- Sofosbuvir
  - AUC: ↔
  - Cmax: ↔

- No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4).
### Medicinal products by therapeutic areas

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Recommendations concerning co-administration with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ombitasvir/Paritaprevir/ritonavir (with or without dasabuvir) / efavirenz/emtricitabine/tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)</strong></td>
<td>Co-administration of efavirenz based regimens with paritaprevir/ritonavir + dasabuvir resulted in ALT elevations. Concomitant use with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets is contraindicated (see section 4.3).</td>
</tr>
<tr>
<td><strong>Simeprevir / efavirenz</strong></td>
<td>Concomitant use with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets is contraindicated (see section 4.3).</td>
</tr>
<tr>
<td><strong>Sofosbuvir (400 mg q.d.) / efavirenz/emtricitabine/tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)</strong></td>
<td>Sofosbuvir AUC: ↔ Cmax: ↓ 19% GS-3310071 AUC: ↔ Cmax: ↓ 23% Efavirenz AUC: ↔ Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets and sofosbuvir can be co-administered without dose adjustment.</td>
</tr>
</tbody>
</table>
## Medicinal products by therapeutic areas

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Recommendations concerning co-administration with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax: ↔</td>
<td></td>
</tr>
<tr>
<td>Cmin: ↔</td>
<td></td>
</tr>
<tr>
<td>Emtricitabine AUC: ↔</td>
<td></td>
</tr>
<tr>
<td>Cmax: ↔</td>
<td></td>
</tr>
<tr>
<td>Cmin: ↔</td>
<td></td>
</tr>
<tr>
<td>Tenofovir AUC: ↔</td>
<td></td>
</tr>
<tr>
<td>Cmax: ↑ 25%</td>
<td></td>
</tr>
<tr>
<td>Cmin: ↔</td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir/velpatasvir (400mg/100mg) / efavirenz/emtricitabine/tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)</td>
<td>Co-administration of Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets with sofosbuvir/velpatasvir is expected to decrease the concentration of velpatasvir. Co-administration with efavirenz-containing regimens is not recommended (see section 4.4).</td>
</tr>
<tr>
<td>Sofosbuvir AUC: ↔</td>
<td></td>
</tr>
<tr>
<td>Cmax: ↑ 20%</td>
<td></td>
</tr>
<tr>
<td>Velpatasvir AUC ↓ 53%</td>
<td></td>
</tr>
<tr>
<td>Cmax ↓ 47%</td>
<td></td>
</tr>
<tr>
<td>Cmin ↓ 57%</td>
<td></td>
</tr>
<tr>
<td>Efavirenz: AUC: ↔</td>
<td></td>
</tr>
<tr>
<td>Cmax: ↔</td>
<td></td>
</tr>
<tr>
<td>Cmin: ↔</td>
<td></td>
</tr>
<tr>
<td>Emtricitabine AUC: ↔</td>
<td></td>
</tr>
<tr>
<td>Cmax: ↔</td>
<td></td>
</tr>
<tr>
<td>Cmin: ↔</td>
<td></td>
</tr>
<tr>
<td>Tenofovir AUC ↓ 40 to 80%</td>
<td></td>
</tr>
<tr>
<td>Cmax ↑ 40 to 80%</td>
<td></td>
</tr>
</tbody>
</table>

### ANTIFUNGALS

<table>
<thead>
<tr>
<th>Ketoconazole (400 mg single dose; efavirenz 600 mg to steady state) / efavirenz</th>
<th>Ketoconazole AUC ↓ 72%</th>
<th>Consider alternative antifungal agent, or use therapeutic drug monitoring (TDM) if available.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itraconazole (200 mg b.i.d) / efavirenz</td>
<td>Itraconazole AUC at steady state ↓ 39%, Cmin ↓ 44%</td>
<td>Consider alternative antifungal agent, or use TDM if available.</td>
</tr>
<tr>
<td>Posaconazole (400 mg b.i.d./400 mg q.d.) / efavirenz</td>
<td>Posaconazole: AUC ↓ 50%, Cmax ↓ 45%</td>
<td>Concomitant use of posaconazole and efavirenz should be avoided.</td>
</tr>
<tr>
<td>Fluconazole (200 mg q.d) / efavirenz</td>
<td>No significant interaction</td>
<td></td>
</tr>
<tr>
<td>Voriconazole (200 b.i.d) / efavirenz</td>
<td>No data available</td>
<td>Efavirenz and voriconazole at standard doses must not be coadministered.</td>
</tr>
</tbody>
</table>
| Voriconazole (200 mg b.i.d.) / efavirenz (400 mg q.d) | Voriconazole AUCss ↓ 77%; Efavirenz AUCss ↑ 44% | The dose reduction for efavirenz with voriconazole at standard dose leads to a significant alteration in the
Medicinal products by therapeutic areas | Interaction | Recommendations concerning co-administration with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets
---|---|---

**Voriconazole** (400 mg b.i.d) / efavirenz 300 mg q.d | Voriconazole AUCss ↓ 7%; Efavirenz AUCss ↑ 17%; both compared with standard doses of voriconazole and efavirenz (200 mg b.i.d and 600 mg q.d, respectively) | If coadministration is considered necessary, voriconazole should be dosed 400 mg b.i.d and efavirenz dosed at 300 mg q.d. As this dose reduction of efavirenz cannot be accommodated for with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets alternative formulations of efavirenz, tenofovir disoproxil and emtricitabine should be used (see section 4.3.)

**Clarithromycin** (500 mg b.i.d, multiple doses) / efavirenz | Clarithromycin AUC ↓ 39%; 14-OH-clarithromycin AUC ↑ 34% | The clinical significance, if any, of these alterations in clarithromycin exposure is not known. A high frequency of rash was seen when the drugs were co-administered in healthy volunteers. Consider azithromycin instead, if possible.

**Azithromycin** (600 mg single dose) / efavirenz (400 mg once daily), | No clinically significant pharmacokinetic interaction | No dosage adjustment is necessary for either medicinal product.

**Rifampicin** (600 mg q.d, multiple doses) / efavirenz | Efavirenz AUC ↓ 26%, Cmin ↓ 32% | When co-treating, a dose increase of efavirenz from 600 mg to 800 mg q.d. should be considered in patients weighing 50 kg or more. Individual tolerability and virological response should be considered when making the dose adjustment. No dose adjustment of rifampicin is recommended when given with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets.

**Rifabutin** (300 mg q.d) / efavirenz | Rifabutin AUCss ↓ 38% | Increase rifabutin dose by 50% if co-treating with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets.

**Atovaquone and proguanil Hydrochloride** / efavirenz (250/100mg single dose/600mgq.d.) Atovaquone and proguanil hydrochloride/emtricitabine | Atovaquone: AUC: ↓ 75% (162 to 184) Cmax: ↓ 144% (120 to 161) Proguanil: AUC: ↓ 43% (47 to 65) | Concomitant administration of atovaquone/proguanil with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets should be avoided whenever possible.
**Medicinal products by therapeutic areas**

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<thead>
<tr>
<th>Interaction</th>
<th>Recommendations concerning co-administration with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atovaquone and proguanil hydrochloride/tenofovir disoproxil</strong></td>
<td>Interaction not studied.</td>
</tr>
<tr>
<td><strong>Chloroquine</strong></td>
<td>No formal interaction studies available. Drug interactions and safety in coadministration with efavirenz has not been systematically evaluated; on a theoretical basis, clinically significant drug interactions with efavirenz are unlikely</td>
</tr>
<tr>
<td><strong>Mefloquine</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Proguanil</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Sulfadoxine</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Pyrimethamine / efavirenz</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Amodiaquine/Artesunate</strong> (600/250 mg q.d.) / efavirenz</td>
<td>An interaction study (EFV at steady-state) was terminated after the first two subjects developed asymptomatic but significant hepatic enzyme elevations after a three-day course of amodiaquine. Amodiaquine AUC ↑ 114 and 302% respectively. Possibly increased hepatic toxicity. Avoid combination.</td>
</tr>
<tr>
<td><strong>Quinine / efavirenz</strong></td>
<td>No formal interaction study available. Quinine is extensively metabolised by CYP3A. Co-administration with efavirenz may decrease quinine exposure, and reduce the antimalarial effect. If possible, an alternative agent to quinine should be used in co-treatment with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets.</td>
</tr>
<tr>
<td><strong>Halofantrine / efavirenz</strong></td>
<td>No formal interaction studies available. These agents are metabolised by CYP3A; hence, co-treatment with efavirenz may decrease exposure (see below) Co-treatment with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets may decrease antimalarial efficacy. When co-treating caution is recommended.</td>
</tr>
<tr>
<td><strong>Artemether/Lumefantrine / efavirenz</strong> (20/120 mg tablet, 6 doses of 4 tablets each over 3 days/600 mg q.d.)</td>
<td>Artemether: AUC: ↓ 51%; Cmax: ↓ 21% Dihydroartemisinin (active metabolite): AUC: ↓ 46%; Cmax: ↓ 38% Lumefantrine: AUC: ↓ 21%; Cmax: ↔; Efavirenz: AUC: ↓ 17%; Cmax: ↔ (CYP3A4 induction) Co-treatment with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets may decrease antimalarial efficacy. When co-treating caution is recommended.</td>
</tr>
</tbody>
</table>

**ANTICONVULSANTS**

| Carbamazepine (400 mg q.d) / efavirenz | Carbamazepine AUCss: ↓ 27%, Cmin ↓ 35%; Co-administration with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets |
### Medicinal products by therapeutic areas

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Recommendations concerning co-administration with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>efavirenz AUCss: ↓ 36%, Cmin ↓ 47%</td>
<td>mg/300 mg Tablets. Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets should be avoided unless plasma concentrations of carbamazepine and efavirenz can be monitored.</td>
</tr>
</tbody>
</table>

**Phenytoin / efavirenz**
- No interaction study available.
- Phenytoin and efavirenz clearance is likely to be increased.

Co-administration should be avoided unless plasma concentrations of phenytoin and efavirenz can be monitored.

**Valproic acid (250 mg b.i.d) / efavirenz**
- No significant interaction is likely.

**Vigabatrin**
- No significant interaction is likely.

Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets and vigabatrin can be co-administered without dose adjustment.

### ANTIDEPRESSANTS

**Selective Serotonin Reuptake Inhibitors (SSRIs)**

**Sertraline / efavirenz**
- Sertraline: AUC: ↓ 39%, Cmin: ↓ 46%
- Efavirenz: AUC: ↔, Cmin: ↔ (CYP3A4 induction)

When co-administered with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets sertraline dose increases should be guided by clinical response.

**CARDIOVASCULAR AGENTS**

**Calcium channel blockers**

**Diltiazem (240 mg q.d.) / efavirenz**
- Diltiazem: AUC: ↓ 69%
- Desacetyl diltiazem: AUC: ↓ 75%
- N-monodesmethyl diltiazem: AUC: ↓ 37%

Monitor the clinical effect of diltiazem and increase dose if necessary.

**Verapamil, felodipine, nifedipine, nicardipine / efavirenz**
- Interaction not studied. Calcium channel blocker exposure is likely to be lowered in co-treatment with efavirenz.

Monitor clinical effect and increase calcium channel blocker dose if necessary.
### Medicinal products by therapeutic areas

#### LIPID LOWERING AGENTS

<table>
<thead>
<tr>
<th>Medication</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atorvastatin</strong> (10 mg q.d) / efavirenz</td>
<td>Atorvastatin: AUC: ↓43% Total active moiety: AUC: ↓34%</td>
<td>Cholesterol levels should be periodically monitored and the dose of atorvastatin increased in case of insufficient efficacy.</td>
</tr>
<tr>
<td><strong>Pravastatin</strong> (40 mg q.d.) / efavirenz</td>
<td>Pravastatin: AUC: ↓40%</td>
<td>Cholesterol levels should be periodically monitored and the dose of pravastatin increased in case of insufficient efficacy.</td>
</tr>
<tr>
<td><strong>Simvastatin</strong> 40 mg q.d. / efavirenz</td>
<td>Simvastatin: AUC: ↓69% Total active moiety: AUC: ↓60%</td>
<td>Cholesterol levels should be periodically monitored and the dose of simvastatin increased in case of insufficient efficacy.</td>
</tr>
<tr>
<td><strong>Rosuvastatin</strong> / efavirenz</td>
<td>Interaction not studied. Rosuvastatin is largely excreted unchanged via the faeces; therefore metabolic drug interaction with efavirenz is not expected.</td>
<td></td>
</tr>
</tbody>
</table>

#### HORMONAL CONTRACEPTIVES

<table>
<thead>
<tr>
<th>Medication</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ethinylestradiol/norgestimate</strong> (0.035 mg + 0.25 mg q.d) / efavirenz</td>
<td>No change in ethinylestradiol exposure. Levonorgestrel AUC ↓83%, norelgestromin AUC ↓64% (active metabolites)</td>
<td>A reliable method of barrier contraception should be used in addition to oral contraceptives.</td>
</tr>
<tr>
<td><strong>DMPA</strong> (150 mg i.m. single dose) / efavirenz</td>
<td>The pharmacokinetics and efficacy of DMPA was not altered due to co-treatment with efavirenz</td>
<td>Because of the limited information available, a reliable method of barrier contraception must be used in addition to hormonal contraception.</td>
</tr>
<tr>
<td><strong>Etonogestrel</strong> (implant) / efavirenz</td>
<td>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</td>
<td>A reliable method of barrier contraception must be used in addition to hormonal contraception.</td>
</tr>
</tbody>
</table>

#### IMMUNOSUPPRESSANTS

<table>
<thead>
<tr>
<th>Medication</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrolimus</td>
<td>Interaction not formally studied. Decreased exposure of these immunosuppressants may be expected when co-treating with efavirenz.</td>
<td>Dose adjustments of the immunosuppressants may be needed. Close monitoring of immunosuppressant drug concentrations for at least 2 weeks</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sirolimus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>/ efavirenz</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicinal products by therapeutic areas</td>
<td>Interaction</td>
<td>Recommendations concerning co-administration with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets</td>
</tr>
<tr>
<td>---------------------------------------</td>
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<td>----------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets</strong> (Strides Shasun Ltd), HA53</td>
<td>(until steady-state concentrations are reached) is recommended when starting or stopping therapy with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets</td>
<td></td>
</tr>
</tbody>
</table>

**OTHERS**

<table>
<thead>
<tr>
<th>Methadone / efavirenz</th>
<th>Methadone AUC ↓ 52%</th>
<th>Monitor for withdrawal symptoms and increase methadone dose if necessary.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine / efavirenz</td>
<td>Buprenorphine AUC ↓ 50%; norbuprenorphine AUC ↓ 71% (active metabolite) Despite these decreases in exposure, no patients in the study exhibited withdrawal symptoms.</td>
<td>Monitor for withdrawal symptoms and increase buprenorphine dose if necessary.</td>
</tr>
</tbody>
</table>
| Bupropion (150mg single dose -sustained release) / efavirenz | Bupropion: 
AUC: ↓55%
C<sub>max</sub>: ↓34%
Hydroxybupropion: 
AUC: ↔
C<sub>max</sub>: ↑50% | Increases in bupropion dosage should be guided by clinical response, but the maximum recommended dose of bupropion should not be exceeded. No dose adjustment is necessary for efavirenz. |
| Bupropion / emtricitabine | Interaction not studied |
| Bupropion / tenofovir disoproxil | Interaction not studied |
| Warfarin / 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. |
| Acenocoumarol / efavirenz | |
| Lorazepam (2mg single dose) / efavirenz | Lorazepam: 
AUC: ↑ 7% | No dose adjustment necessary |
| Midazolam | No interaction study available |
| Triazolam / efavirenz | These benzodiazepines are metabolised by CYP3A. While efavirenz is an inducer of CYP3A in vivo, it acts as an inhibitor in vitro. The impact of co-administration on midazolam and triazolam pharmacokinetics is unknown. Co-administer with caution. |
| St. John’s Wort (hypericum perforatum) / efavirenz | No interaction study available | Concomitant treatment is contra-indicated. Co-administration is likely to decrease efavirenz levels and to precipitate virological failure. |
Cannabinoid test interaction
Efavirenz does not bind to cannabinoid receptors. False-positive urine cannabinoid test results have been reported with some screening assays in uninfected and HIV-infected subjects receiving efavirenz. Confirmatory testing by a more specific method such as gas chromatography/mass spectrometry is recommended in such cases.

4.6 Fertility, pregnancy and lactation

Pregnancy
Cases of neural tube defects in infants born to women with first trimester exposure have been reported. A meta-analysis of observational cohorts found no increased risk of overall birth defects in over 2,000 pregnancy outcomes exposed to efavirenz compared with exposure to other antiretroviral drugs. In this analysis the incidence of neural tube defects was low, 0.05% (95% CI < 0.01–0.28), and similar to incidence in the general population. However, risks to the foetus cannot be ruled out (see section 5.3).
In humans, the safety of tenofovir and emtricitabine in pregnancy has not been fully established. Sufficient numbers of first trimester exposures have been monitored, however, to detect at least a twofold increase in the risk of overall birth defects. No increase in birth defects was seen (www.apregistry.com). Animal studies do not indicate any harmful effects of tenofovir disoproxil or emtricitabine with respect to pregnancy, foetal development, parturition or postnatal development (see section 5.3).
Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets can be used during pregnancy, if the benefit is considered to outweigh the risk.
Current recommendations on HIV and pregnancy (e.g. those from the WHO) should be consulted before advising patients on this matter.

Breastfeeding
Efavirenz, emtricitabine and tenofovir have been shown to be excreted in human milk. There is insufficient information on the effects of efavirenz, emtricitabine and tenofovir in newborns/infants. A risk to the infants cannot be excluded.
Current recommendations on HIV and breastfeeding (e.g. those from the WHO) should be consulted before advising patients on this matter. Preferred options may vary depending on the local circumstances.

Fertility
No human data on the effect of Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets are available. Animal studies do not indicate harmful effects of efavirenz, emtricitabine or tenofovir disoproxil on fertility.

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. However, dizziness has been reported during treatment with efavirenz, emtricitabine and tenofovir disoproxil. Efavirenz may also cause impaired concentration and/or somnolence. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving and operating machinery.

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

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

Rare events of renal impairment, renal failure and proximal renal tubulopathy (including Fanconi syndrome) sometimes leading to bone abnormalities (infrequently contributing to fractures) have also been reported. Monitoring of renal function is recommended for patients receiving Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets (see section 4.4).

Discontinuation Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis (see section 4.4).

The administration of Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets with food may increase efavirenz exposure and may lead to an increase in the frequency of adverse reactions (see sections 4.4 and 5.2).

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

The adverse reactions from clinical studies and post-marketing experience are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000. In addition, adverse events identified during post-approval use are listed (frequency category: ‘not known’). Since they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Blood and lymphatic system disorders:
Common: neutropenia
Uncommon: anaemia

Immune system disorders
Common: allergic reaction
Uncommon: hypersensitivity

Metabolic and nutrition disorders
Very common: hypophosphataemia
Common: hypertriglyceridaemia, hyperglycaemia
Uncommon: hypercholesterolaemia, hypokalaemia
Rare: lactic acidosis

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

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

Eye disorders
Uncommon: blurred vision.

Ear and labyrinth disorders
Uncommon: tinnitus, vertigo.

Vascular disorders
Uncommon: flushing

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

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

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

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

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

Reproductive system and breast disorders
Uncommon: gynaecomastia, libido decreased.

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

General disorders and administration site disorders
Very common: asthenia
Common: pain, fatigue.
* These adverse reactions were identified through post-marketing surveillance for either efavirenz, emtricitabine or tenofovir disoproxil. The frequency category was estimated from a statistical calculation based on the total number of patients treated with any of the components of this fixed dose combination.

**Description of selected adverse reactions**

**Rash**
In clinical trials of efavirenz, rashes were usually mild-to-moderate maculopapular skin eruptions that occurred within the first two weeks of initiating therapy with efavirenz. In most patients, rash resolved with continuing therapy with efavirenz within one month. Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets can be reinitiated in patients interrupting therapy because of rash. Use of appropriate antihistamines and/or corticosteroids is recommended when Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets is restarted.

**Nervous system symptoms**
Nervous system symptoms are common with efavirenz, one of the components of Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets. In clinical studies of efavirenz, nervous system symptoms of moderate to severe intensity were experienced by 19% (severe 2%) of patients, and 2% of patients discontinued therapy due to such symptoms. They usually begin during the first one or two days of efavirenz therapy and generally resolve after the first two to four weeks. They may occur more frequently when dosing without meals and at bedtime seems to improve the tolerability of these symptoms (see sections 4.2 and 5.2).

**Renal impairment**
As Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets may cause renal damage, monitoring of renal function is recommended (see sections 4.4 and 4.8 Summary of the safety profile). Proximal renal tubulopathy generally resolved or improved after tenofovir disoproxil discontinuation. Patients at risk of renal impairment (such as patients with baseline renal risk factors, advanced HIV disease, or patients receiving concomitant nephrotoxic medications) are at increased risk of experiencing incomplete recovery of renal function despite tenofovir disoproxil discontinuation (see section 4.4).

**Renal tubulopathy**
The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy due to tenofovir disoproxil: rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), hypokalaemia, muscular weakness, myopathy and hypophosphataemia. These events are not considered to be causally associated with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets in the absence of proximal renal tubulopathy.

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

**Interaction with didanosine**
Co-administration of Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets and didanosine is not recommended as it results in a 40-60% increase in systemic exposure to didanosine that may increase the risk of didanosine-related adverse reactions (see section 4.5). Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported.

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

Immune Reactivation Syndrome
In HIV infected patients with severe immune deficiency at the time of initiation of CART, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves’ disease) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Osteonecrosis
Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to CART. The frequency of this is unknown (see section 4.4).

Osteonecrosis
Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to CART. The frequency of this is unknown (see section 4.4).

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

Osteonecrosis
Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to CART. The frequency of this is unknown (see section 4.4).

Older people
The combination of efavirenz, emtricitabine and tenofovir disoproxil has not been studied in patients over the age of 65. Older people are more likely to have decreased hepatic or renal function. Therefore caution should be exercised when treating older people with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets (see section 4.2).

Patients with renal impairment:
Since tenofovir disoproxil can cause renal toxicity, close monitoring of renal function is recommended in any patient with mild renal impairment treated with Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets (see sections 4.2, 4.4 and 5.2).

HIV/HBV or HCV co-infected patients:
Clinical studies included only a limited number of patients co-infected with HBV or HCV. The adverse reaction profile of efavirenz, emtricitabine and tenofovir disoproxil in patients co-infected with HIV/HBV or HIV/HCV was similar to that observed in patients infected with HIV without co-infection. However, as would be expected in this patient population, elevations in AST and ALT occurred more frequently than in the general HIV infected population.

Exacerbations of hepatitis after discontinuation of treatment:
In HIV infected patients co-infected with HBV, clinical and laboratory evidence of hepatitis may occur after discontinuation of treatment (see section 4.4).

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.
4.9 Overdose

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

Management
If overdose occurs the patient must be monitored for evidence of toxicity (see sections 4.8 and 5.3), and standard supportive treatment applied as necessary.

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

Up to 30% of the emtricitabine dose and approximately 10% of the tenofovir dose can be removed by haemodialysis. It is not known whether emtricitabine or tenofovir can be removed by peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action and pharmacodynamic effect:
Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. Efavirenz binds directly to reverse transcriptase and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by inducing a conformational change that causes a disruption of the enzyme's catalytic site. The activity of efavirenz does not compete with template or nucleoside triphosphates. HIV-2 reverse transcriptase and eukaryotic DNA polymerases (such as human DNA polymerases α, β, γ, or δ) are not inhibited by efavirenz. Emtricitabine is an analogue of the nucleoside cytidine. Tenofovir disoproxil is converted in vivo to tenofovir, a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate. Emtricitabine and tenofovir are phosphorylated by cellular enzymes to form emtricitabine triphosphate and tenofovir diphosphate, respectively.

Emtricitabine triphosphate and tenofovir diphosphate competitively inhibit HIV-1 reverse transcriptase (RT), resulting in DNA chain termination. Both substances are active against HIV-1 and HIV-2, as well as against hepatitis B virus.
Both emtricitabine triphosphate and tenofovir diphosphate are weak inhibitors of mammalian DNA polymerases and there was no evidence of toxicity to mitochondria in vitro and in vivo.

Antiviral activity in vitro
Efavirenz demonstrated antiviral activity against most non-clade B isolates (subtypes A, AE, AG, C, D, F, G, J, and N) but had reduced antiviral activity against group O viruses. Emtricitabine displayed antiviral activity against HIV-1 clades A, B, C, D, E, F, and G. Tenofovir displayed antiviral activity against HIV-1 clades A, B, C, D, E, F, G, and O. Both emtricitabine and tenofovir showed strain specific activity against HIV-2 and antiviral activity against HBV.
In combination studies evaluating the in vitro antiviral activity of efavirenz and emtricitabine together, efavirenz and tenofovir together, and emtricitabine and tenofovir together, additive to synergistic antiviral effects were observed.
Resistance

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

HIV-1 resistance to emtricitabine develops as the result of the M184V mutation in the RT. This HIV-1 mutation was observed in vitro and in HIV-1 infected patients. Emtricitabine-resistant viruses were cross-resistant to lamivudine, but retained sensitivity to other nucleoside reverse transcriptase inhibitors (NRTIs) (zidovudine, stavudine, tenofovir, abacavir, didanosine and zalcitabine), all non-nucleoside reverse transcriptase inhibitors (NNRTIs) and all protease inhibitors (PIs).

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

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

Clinical results

When tenofovir disoproxil and emtricitabine were combined with efavirenz in treatment-naïve adult patients with HIV-1, the proportion of patients (ITT) with HIV-RNA <50 copies/ml were 80 and 64% at 48 and 144 weeks, respectively. In another study, were tenofovir disoproxil and emtricitabine were combined with lopinavir/ritonavir given once or twice daily in treatment naive patients, 70% and 64% of patients demonstrated HIV-1 RNA < 50 copies/ml with the once and twice daily regimens of lopinavir/ritonavir, respectively.

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

Patients coinfected with HIV and HBV

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

5.2 Pharmacokinetic properties

Efavirenz

Absorption and Bioavailability

Bioavailability is 40% to 45% without food. Food increases absorption significantly. Time to peak plasma concentrations (3 - 5 hours) did not change following multiple dosing and steady-state plasma concentrations were reached in 6 - 7 days.
Following single dose of administration of Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets in healthy volunteers, mean (±SD) efavirenz Cmax value was 2324(±763)ng/ml and the corresponding value for AUC0-72h was 55153(±21306)ng.h/ml. The median efavirenz tmax value was 4.34(± 0.97) hours.

**Distribution**

Efavirenz is highly bound (more than 99%) to human plasma proteins, predominantly albumin. In HIV-1 infected patients who received efavirenz 200 to 600 mg once daily for at least one month, mean cerebrospinal fluid concentrations 0.69% of the corresponding plasma concentration were reached. This proportion is approximately 3-fold higher than the non-protein-bound (free) fraction of efavirenz in plasma.

**Metabolism**

Efavirenz is principally metabolised by the cytochrome P450 system to hydroxylated metabolites. These metabolites are essentially inactive against HIV-1. In vitro studies, supported by in vivo observations, suggest that CYP3A4 and CYP2B6 are the major isoforms responsible for efavirenz metabolism. Efavirenz has been shown to induce cytochrome P450 enzymes, resulting in the induction of its own metabolism.

**Elimination**

Efavirenz has a relatively long terminal half-life of 17 to 154 hours after single doses, and 40 - 55 hours after multiple doses. In individuals with certain mutant CYP2B6 genotypes (e.g. the T/T genotype at G516T) the terminal half-life may be substantially prolonged, and drug exposures higher. These genotypes are particularly common among Africans and African Americans. In patients with liver impairment, lower efavirenz clearance and higher drug exposures have been reported. Approximately 14 - 34% of a radio-labelled dose of efavirenz was recovered in the urine and less than 1% of the dose was excreted in urine as unchanged efavirenz.

**Emtricitabine:**

**Absorption**

The absolute bioavailability of emtricitabine has been estimated to 75-93%. Administration of emtricitabine with or without food did not affect systemic exposure.

Following single dose administration of Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets in healthy volunteers, the mean (±SD) emtricitabine Cmax value was 1861(±396) ng/ml and the corresponding value for AUC was 10678(±2503) ng.h/ml. The mean (±SD) emtricitabine Tmax value was 1.81 (±0.87) hours.

**Distribution**

In vitro binding of emtricitabine to human plasma proteins was < 4% and independent of concentration over the range of 0.02-200 μg/ml. The apparent volume of distribution after intravenous administration of emtricitabine was 1.4±0.3 l/kg.

**Elimination**

Emtricitabine is primarily excreted by the kidneys with complete recovery of the dose achieved in urine (approximately 86%) and faeces (approximately 14%). Thirteen percent of the emtricitabine dose was recovered in urine as three metabolites. The systemic clearance of emtricitabine averaged 307 ml/min (4.03 ml/min/kg). Following oral administration, the elimination half-life of emtricitabine is approximately 10 hours.

**Intracellular pharmacokinetics:** In a clinical study, the intracellular half-life of emtricitabine-triphosphate in peripheral blood mononuclear cells was 39 hours. Intracellular triphosphate levels increased with dose, but reached a plateau at doses of 200 mg or greater.

**Adults with renal insufficiency:** Pharmacokinetic parameters were determined following administration of a single dose of 200 mg emtricitabine hard capsules to 30 non-HIV infected subjects with varying degrees of
renal insufficiency. Subjects were grouped according to baseline creatinine clearance (> 80 ml/min as normal function; 50-80 ml/min as mild impairment; 30-49 ml/min as moderate impairment; < 30 ml/min as severe impairment; < 15 ml/min as functionally anephric requiring haemodialysis). The systemic emtricitabine exposure (mean ± standard deviation) increased from 11.8±2.9 μg·h/ml in subjects with normal renal function to 19.9±1.1, 25.0±5.7 and 34.0±2.1 μg·h/ml, in patients with mild, moderate and severe renal impairment, respectively.

In patients with ESRD on haemodialysis, approximately 30% of the emtricitabine dose was recovered in dialysate over a 3 hour dialysis period which had been started within 1.5 hours of emtricitabine dosing (blood flow rate of 400 ml/min and dialysate flow rate of approximately 600 ml/min).

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

Pharmacokinetic data are not available in the elderly.

**Tenofovir disoproxil fumarate**

Tenofovir disoproxil fumarate is a water-soluble ester prodrug, which is rapidly converted in vivo to tenofovir and formaldehyde. Tenofovir is converted intracellularly to tenofovir monophosphate and to the active component, tenofovir diphosphate.

**Absorption**

Following oral administration of tenofovir disoproxil fumarate to HIV infected patients, tenofovir disoproxil fumarate is rapidly absorbed and converted to tenofovir. The oral bioavailability of tenofovir from tenofovir disoproxil fumarate in fasted patients was approximately 25%. Administration of tenofovir disoproxil fumarate with a high fat meal enhanced the oral bioavailability, with an increase in tenofovir AUC by approximately 40% and Cmax by approximately 14%.

Following single dose administration of Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600 mg/200 mg/300 mg Tablets in healthy volunteers, the mean (±SD) tenofovir Cmax value was 342(±82) ng/ml and the corresponding value for AUC was 2165(±510) ng·h/ml. The mean (±SD) tenofovir tmax value was 1.18 (± 0.64) hours.

**Distribution**

Following intravenous administration the steady-state volume of distribution of tenofovir was estimated to be approximately 800 ml/kg. In vitro protein binding of tenofovir to plasma or serum protein was less than 0.7 and 7.2%, respectively, over the tenofovir concentration range 0.01 to 25 μg/ml.

**Elimination**

Tenofovir is primarily excreted by the kidney, both by filtration and an active tubular transport system with approximately 70-80% of the dose excreted unchanged in urine following intravenous administration. Total clearance has been estimated to be approximately 230 ml/h/kg (approximately 300 ml/min).

Renal clearance has been estimated to be approximately 160 ml/h/kg (approximately 210 ml/min), which is in excess of the glomerular filtration rate. This indicates that active tubular secretion is an important part of the elimination of tenofovir. Following oral administration the terminal half-life of tenofovir is approximately 12 to 18 hours.

Studies have established the pathway of active tubular secretion of tenofovir to be influx into proximal tubule cell by the human organic anion transporters (hOAT) 1 and 3 and efflux into the urine by the multidrug resistant protein 4 (MRP 4). In vitro studies have determined that neither tenofovir disoproxil fumarate nor tenofovir are substrates for the CYP450 enzymes.

**Age and gender**

Limited data on the pharmacokinetics of tenofovir in women indicate no major gender effect.
Tenofovir exposure achieved in adolescent patients receiving oral daily doses of tenofovir 300 mg was similar to exposures achieved in adults receiving once-daily doses of tenofovir 300 mg.

Pharmacokinetic studies have not been performed in children or in the elderly (over 65 years). Pharmacokinetics have not been specifically studied in different ethnic groups.

Renal impairment
Pharmacokinetic parameters of tenofovir were determined following administration of a single dose of tenofovir disoproxil fumarate 300 mg to 40 non-HIV, non-HBV infected patients with varying degrees of renal impairment defined according to baseline creatinine clearance (CrCl) (normal renal function when CrCl > 80 ml/min; mild with CrCl = 50-79 ml/min; moderate with CrCl = 30-49 ml/min and severe with CrCl = 10-29 ml/min). Compared with patients with normal renal function, the mean (%CV) tenofovir exposure increased from 2,185 (12%) ng·h/ml in subjects with CrCl > 80 ml/min to respectively 3,064 (30%) ng·h/ml, 6,009 (42%) ng·h/ml and 15,985 (45%) ng·h/ml in patients with mild, moderate and severe renal impairment. The dosing recommendations in patients with renal impairment, with increased dosing interval, are expected to result in higher peak plasma concentrations and lower Cmin levels in patients with renal impairment compared with patients with normal renal function. The clinical implications of this are unknown.

In patients with end-stage renal disease (ESRD) (CrCl < 10 ml/min) requiring haemodialysis, between dialysis tenofovir concentrations substantially increased over 48 hours achieving a mean Cmax of 1,032 ng/ml and a mean AUC0-48h of 42,857 ng·h/ml. It is recommended that the dosing interval for tenofovir disoproxil fumarate 300 mg is modified in patients with creatinine clearance < 50 ml/min or in patients who already have ESRD and require dialysis (see section 4.2).

The pharmacokinetics of tenofovir in non-haemodialysis patients with creatinine clearance < 10 ml/min and in patients with ESRD managed by peritoneal or other forms of dialysis have not been studied.

Hepatic impairment
A single 300 mg dose of tenofovir disoproxil fumarate was administered to non-HIV, non-HBV infected patients with varying degrees of hepatic impairment defined according to Child-Pugh-Turcotte (CPT) classification. Tenofovir pharmacokinetic parameters were not substantially altered in subjects with hepatic impairment suggesting that no dose adjustment is required in these subjects. The mean (%CV) tenofovir Cmax and AUC0-∞ values were 223 (34.8%) ng/ml and 2,05 (50.8%) ng·h/ml, respectively, in normal subjects compared with 289 (46.0%) ng/ml and 2,31 (43.5%) ng·h/ml in subjects with moderate hepatic impairment, and 305 (24.8%) ng/ml and 2,74 (44.0%) ng·h/ml in subjects with severe hepatic impairment.

Intracellular pharmacokinetics
Tenofovir diphosphate has an intracellular half-life of 10 hours in activated and 50 hours in resting peripheral blood mononuclear cells (PBMCs).

5.3 Preclinical safety data

Efavirenz
Non-clinical safety pharmacology studies on efavirenz reveal no special hazard for humans. In repeated-dose toxicity studies, biliary hyperplasia was observed in cynomolgus monkeys given efavirenz for ≥ 1 year at a dose resulting in mean AUC values approximately 2-fold greater than those in humans given the recommended dose. The biliary hyperplasia regressed upon cessation of dosing. Biliary fibrosis has been observed in rats. Non-sustained convulsions were observed in some monkeys receiving efavirenz for ≥ 1 year, at doses yielding plasma AUC values 4- to 13-fold greater than those in humans given the recommended dose.

Efavirenz was not mutagenic or clastogenic in conventional genotoxicity assays.
Carcinogenicity studies showed an increased incidence of hepatic and pulmonary tumours in female mice, but not in male mice. The mechanism of tumour formation and the potential relevance for humans are not known. Carcinogenicity studies in male mice, male and female rats were negative.
Reproductive toxicity studies showed increased foetal resorptions in rats. No malformations were observed in foetuses from efavirenz-treated rats and rabbits. However, malformations were observed in 3 of 20 foetuses/newborns from efavirenz-treated cynomolgus monkeys given doses resulting in plasma efavirenz concentrations similar to those seen in humans. Anencephaly and unilateral anophthalmia with secondary enlargement of the tongue were observed in one foetus, microphthalmia was observed in another foetus and cleft palate was observed in a third foetus.

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

**Tenofovir disoproxil**
Non-clinical safety pharmacology studies on tenofovir disoproxil reveal no special hazard for humans. Findings in repeated-dose toxicity studies in rats, dogs and monkeys at exposure levels greater than or equal to clinical exposure levels and with possible relevance to clinical use include renal and bone toxicity and a decrease in serum phosphate concentration. Bone toxicity was diagnosed as osteomalacia (monkeys) and reduced bone mineral density (BMD) (rats and dogs). The 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). Findings in the rat and monkey studies indicated that there was a substance-related decrease in intestinal absorption of phosphate with potential secondary reduction in BMD.

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

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

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

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

### 6. PHARMACEUTICAL PARTICULARS
#### 6.1 List of Excipients

Core tablet:
- Microcrystalline cellulose, lactose, croscarmellose sodium, sodium lauryl sulfate, hydroxypropyl cellulose, magnesium stearate

Film coat:
- Polyvinyl alcohol (partly hydrolysed), macrogol/PEG, titanium dioxide, talc, FD&C blue #2 indigo carmine aluminium lake

#### 6.2 Incompatibilities
Not applicable.

#### 6.3 Shelf life
24 months.
6.4 Special precautions for storage
Do not store above 25°C. Keep in a tightly closed container.

6.5 Nature and contents of container
A white opaque HDPE bottle (100 cc) with white opaque HDPE screw closure with 7 layered induction
sealing liner printed “sealed for your protection”. The bottle also contains a 2.0 g of silica gel sachet as
desiccant.
Pack size: 30 tablets

6.6 Special precautions for disposal
No special requirements.
Any unused product or waste material should be disposed off in accordance with local requirements.

7. SUPPLIER
Strides Shasun Limited
Strides House, Bilekahalli
Bannerghatta Road
Bangalore – 560 076
India

8. WHO REFERENCE NUMBER (PREQUALIFICATION PROGRAMME)
HA553

9. DATE OF FIRST PREQUALIFICATION/ LAST RENEWAL
12 December 2014

10. DATE OF REVISION OF THE TEXT:
May 2017

Detailed information on this medicinal product is available on the website of the WHO Prequalification
Programme https://extranet.who.int/prequal/

References
General reference sources for this SmPC include:

WHO Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection;
Recommendations for a public health approach - Second edition, available at http://www.who.int/hiv/pub/arv/arv-
2016/en/

European SmPC Atripla. Available at:

Further references relevant to specific sections of the SmPC include:
Section 4.5

All weblinks were last accessed 12 April 2017