ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Efavirenz/Emtricitabine/Tenofovir disoproxil Krka 600 mg/200 mg/245 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 600 mg of efavirenz (efavirenzum), 200 mg of emtricitabine (emtricitabinum) and 245 mg of tenofovir disoproxil (tenofovirum disoproxilum) (as succinate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Tablets are light orange pink, oval, biconvex, film-coated tablets with beveled edges. Tablet dimension: 20 x 11 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Efavirenz/Emtricitabine/Tenofovir disoproxil Krka is a fixed-dose combination of efavirenz, emtricitabine and tenofovir disoproxil. It is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults aged 18 years and over with virologic suppression to HIV-1 RNA levels of < 50 copies/ml on their current combination antiretroviral therapy for more than three months. Patients must not have experienced virological failure on any prior antiretroviral therapy and must be known not to have harboured virus strains with mutations conferring significant resistance to any of the three components contained in Efavirenz/Emtricitabine/Tenofovir disoproxil Krka prior to initiation of their first antiretroviral treatment regimen (see sections 4.4 and 5.1).

The demonstration of the benefit of efavirenz/emtricitabine/tenofovir disoproxil is primarily based on 48-week data from a clinical study in which patients with stable virologic suppression on a combination antiretroviral therapy changed to efavirenz/emtricitabine/tenofovir disoproxil (see section 5.1). No data are currently available from clinical studies with efavirenz/emtricitabine/tenofovir disoproxil in treatment-naïve or in heavily pretreated patients.

No data are available to support the combination of efavirenz/emtricitabine/tenofovir disoproxil and other antiretroviral agents.

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the management of HIV infection.

Posology

Adults
The recommended dose of Efavirenz/Emtricitabine/Tenofovir disoproxil Krka is one tablet taken orally once daily.

If a patient misses a dose of Efavirenz/Emtricitabine/Tenofovir disoproxil Krka within 12 hours of the time it is usually taken, the patient should take Efavirenz/Emtricitabine/Tenofovir disoproxil Krka as

soon as possible and resume the normal dosing schedule. If a patient misses a dose of Efavirenz/Emtricitabine/Tenofovir disoproxil Krka by more than 12 hours and it is almost time for the next dose, the patient should not take the missed dose and simply resume the usual dosing schedule.

If the patient vomits within 1 hour of taking Efavirenz/Emtricitabine/Tenofovir disoproxil Krka, another tablet should be taken. If the patient vomits more than 1 hour after taking Efavirenz/Emtricitabine/Tenofovir disoproxil Krka he/she does not need to take another dose.

It is recommended that Efavirenz/Emtricitabine/Tenofovir disoproxil Krka 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 to efavirenz with respect to adverse reactions on the nervous system, bedtime dosing is recommended (see section 4.8).

It is anticipated that tenofovir exposure (AUC) will be approximately 30% lower following administration of efavirenz/emtricitabine/tenofovir disoproxil on an empty stomach as compared to the individual component tenofovir disoproxil when taken with food (see section 5.2). Data on the clinical translation of the decrease in pharmacokinetic exposure are not available. In virologically suppressed patients, the clinical relevance of this reduction can be expected to be limited (see section 5.1).

Where discontinuation of therapy with one of the components of efavirenz/emtricitabine/tenofovir disoproxil is indicated or where dose modification is necessary, separate preparations of efavirenz, emtricitabine and tenofovir disoproxil are available. Please refer to the Summary of Product Characteristics for these medicinal products.

If therapy with efavirenz/emtricitabine/tenofovir disoproxil is discontinued, consideration should be given to the long half-life of efavirenz (see section 5.2) and long intracellular half-lives of emtricitabine and tenofovir. 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.

Dose adjustment: If efavirenz/emtricitabine/tenofovir disoproxil is co-administered with rifampicin to patients weighing 50 kg or more, an additional 200 mg/day (800 mg total) of efavirenz may be considered (see section 4.5).

Special populations

Elderly
Efavirenz/Emtricitabine/Tenofovir disoproxil Krka should be administered with caution to elderly patients (see section 4.4).

Renal impairment
Efavirenz/emtricitabine/tenofovir disoproxil 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 that cannot be achieved with the combination tablet (see sections 4.4 and 5.2).

Hepatic impairment
The pharmacokinetics of efavirenz/emtricitabine/tenofovir disoproxil have not been studied in patients with hepatic impairment. Patients with mild liver disease (Child-Pugh-Turcotte (CPT), Class A) may be treated with the normal recommended dose of efavirenz/emtricitabine/tenofovir disoproxil (see sections 4.3, 4.4 and 5.2). 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 is discontinued in patients co-infected with HIV and hepatitis B virus (HBV), these patients should be closely monitored for evidence of exacerbation of hepatitis (see section 4.4).

Paediatric population
The safety and efficacy of efavirenz/emtricitabine/tenofovir disoproxil in children under the age of 18 years have not been established (see section 5.2).

Method of administration

Efavirenz/Emtricitabine/Tenofovir disoproxil Krka tablets should be swallowed whole with water, once daily.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

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

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

Co-administration with elbasvir/grazoprevir due to the expected significant decreases in plasma concentrations of elbasvir and grazoprevir. This effect is due to induction of CYP3A4 or P-gp by efavirenz and may result in loss of therapeutic effect of elbasvir/grazoprevir (see section 4.5).

Co-administration with voriconazole. Efavirenz significantly decreases voriconazole plasma concentrations while voriconazole also significantly increases efavirenz plasma concentrations. Since efavirenz/emtricitabine/tenofovir disoproxil is a fixed dose combination product, the dose of efavirenz cannot be altered (see section 4.5).

Co-administration with herbal preparations containing St. John's wort (*Hypericum perforatum*) due to the risk of decreased plasma concentrations and reduced clinical effects of efavirenz (see section 4.5).

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

Co administration with medicinal products that are known to prolong the QTc interval (proarrhythmic).
These medicinal products include:
- antiarrhythmics of classes IA and III,
- neuroleptics, antidepressive agents,
- certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole and triazole antifungal agents,
- certain non-sedating antihistamines (terfenadine, astemizole),
- cisapride,
- flecainide,
- certain antimalarials,
- methadone (see sections 4.4, 4.5 and 5.1).

4.4 Special warnings and precautions for use

Co-administration with other medicinal products

As a fixed combination, efavirenz/emtricitabine/tenofovir disoproxil should not be administered concomitantly with other medicinal products containing the same active components, emtricitabine or tenofovir disoproxil. Efavirenz/emtricitabine/tenofovir disoproxil 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 should not be administered concomitantly with other cytidine analogues, such as lamivudine (see section 4.5). Efavirenz/emtricitabine/tenofovir disoproxil should not be administered concomitantly with adefovir dipivoxil or with medicinal products containing tenofovir alafenamide.

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

Co-administration of efavirenz/emtricitabine/tenofovir disoproxil and sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir is not recommended since plasma concentrations of velpatasvir and voxilaprevir are expected to decrease following co-administration with efavirenz leading to reduced therapeutic effect of sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir (see section 4.5).

No data are available on the safety and efficacy of efavirenz/emtricitabine/tenofovir disoproxil in combination with other antiretroviral agents.

Concomitant use of Ginkgo biloba extracts is not recommended (see section 4.5).

Switching from a protease inhibitor (PI)-based antiretroviral regimen

Currently available data indicate a trend that in patients on a PI-based antiretroviral regimen the switch to efavirenz/emtricitabine/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 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 physicians experienced in the treatment of patients with HIV associated diseases.

Effect of food

The administration of efavirenz/emtricitabine/tenofovir disoproxil 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 be taken on an empty stomach, preferably at bedtime.

Liver disease

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

Hepatic events
Post-marketing reports of hepatic failure also occurred in patients with no pre-existing hepatic disease or other identifiable risk factors (see section 4.8). Liver enzyme monitoring should be considered for all patients independent of 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 CART are at an increased risk for severe and potentially fatal hepatic adverse reactions.

Physicians 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 efavirenz/emtricitabine/tenofovir disoproxil have not been studied for the treatment of chronic HBV infection. Emtricitabine and tenofovir individually and in combination have shown activity against HBV in pharmacodynamic studies (see section 5.1). Limited clinical experience suggests that emtricitabine and tenofovir disoproxil have an anti-HBV activity when used in antiretroviral combination therapy to control HIV infection. Discontinuation of efavirenz/emtricitabine/tenofovir disoproxil therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis. Patients co-infected with HIV and HBV who discontinue efavirenz/emtricitabine/tenofovir disoproxil must be closely monitored with both clinical and laboratory follow-up for at least four months after stopping treatment with efavirenz/emtricitabine/tenofovir disoproxil. If appropriate, resumption of anti-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.

<u>QTc prolongation</u>

QTc prolongation has been observed with the use of efavirenz (see sections 4.5 and 5.1). For patients at increased risk of Torsade de Pointes or who are receiving medicinal products with a known risk for Torsade de Pointes, consider alternatives to efavirenz/emtricitabine/tenofovir disoproxil.

<u>Psychiatric symptoms</u>

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 psychosis-like behaviour, and catatonia. Patients should be advised that if they experience symptoms such as severe depression, psychosis or suicidal ideation, they should contact their doctor immediately to assess the possibility 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 adverse reactions in patients receiving efavirenz 600 mg daily 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.

Seizures

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 medicinal product 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 impairment

Efavirenz/emtricitabine/tenofovir disoproxil is not recommended for patients with moderate or severe renal impairment (creatinine clearance < 50 ml/min). Patients with moderate or severe renal impairment require a dose adjustment of emtricitabine and tenofovir disoproxil that cannot be achieved with the combination tablet (see sections 4.2 and 5.2). Use of efavirenz/emtricitabine/tenofovir disoproxil should be avoided with concurrent or recent use of a nephrotoxic medicinal product. If concomitant use of efavirenz/emtricitabine/tenofovir disoproxil 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 is co-administered with an NSAID, renal function should be monitored adequately.

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).

It is recommended that creatinine clearance is calculated in all patients prior to initiating therapy with efavirenz/emtricitabine/tenofovir disoproxil and renal function (creatinine clearance and serum phosphate) is also monitored after two to four weeks of treatment, after three months of treatment and every three to six months thereafter in patients without renal risk factors. In patients with a history of renal dysfunction or in patients who are at risk of renal dysfunction, a more frequent monitoring of renal function is required.

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 efavirenz/emtricitabine/tenofovir disoproxil, renal function must be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations (see section 4.8, proximal tubulopathy). Since efavirenz/emtricitabine/tenofovir disoproxil is a combination product and the dosing interval of the individual components cannot be altered, treatment with efavirenz/emtricitabine/tenofovir disoproxil must be interrupted in patients

with confirmed creatinine clearance < 50 ml/min or decreases in serum phosphate to < 1.0 mg/dl (0.32 mmol/l). Interrupting treatment with efavirenz/emtricitabine/tenofovir disoproxil 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 is indicated or where dose modification is necessary, separate preparations of efavirenz, emtricitabine and tenofovir disoproxil are available.

Bone effects

In a 144-week controlled clinical study (GS-99-903) that compared tenofovir disoproxil with stavudine in combination with lamivudine and efavirenz in antiretroviral-naïve patients, small decreases in bone mineral density (BMD) of the hip and spine were observed in both treatment groups. Decreases in BMD of spine and changes in bone biomarkers from baseline were significantly greater in the tenofovir disoproxil treatment group at 144 weeks. Decreases in BMD 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 this study.

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

Bone abnormalities such as osteomalacia which can manifest as persistent or worsening bone pain, and which can infrequently contribute to fractures, may be associated with tenofovir disoproxil-induced proximal renal tubulopathy (see section 4.8).

Tenofovir disoproxil may also cause a reduction in bone mineral density (BMD).

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

Skin reactions

Mild-to-moderate rash has been reported with the individual components of efavirenz/emtricitabine/tenofovir disoproxil. The rash associated with the efavirenz component usually resolves with continued therapy. Appropriate antihistamines and/or corticosteroids may improve tolerability and hasten the resolution of rash. Severe rash associated with blistering, moist desquamation or ulceration has been reported in less than 1% of patients treated with efavirenz (see section 4.8). The incidence of erythema multiforme or Stevens-Johnson syndrome was approximately 0.1%. Efavirenz/emtricitabine/tenofovir disoproxil must be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. Experience with efavirenz in patients who discontinued other antiretroviral agents of the non-nucleoside reverse transcriptase inhibitor (NNRTI) class is limited. Efavirenz/emtricitabine/tenofovir disoproxil 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, particulary 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 and autoimmune hepatitis) 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.

Osteonecrosis

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

Patients with HIV-1 harbouring mutations

Efavirenz/emtricitabine/tenofovir disoproxil should be avoided in patients with HIV-1 harbouring the K65R, M184V/I or K103N mutation (see sections 4.1 and 5.1).

Elderly

Efavirenz/emtricitabine/tenofovir disoproxil has not been studied in patients over the age of 65. Elderly patients are more likely to have decreased hepatic or renal function, therefore caution should be exercised when treating elderly patients with efavirenz/emtricitabine/tenofovir disoproxil (see section 4.2).

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

As efavirenz/emtricitabine/tenofovir disoproxil contains efavirenz, emtricitabine and tenofovir disoproxil, any interactions that have been identified with these agents individually may occur with

efavirenz/emtricitabine/tenofovir disoproxil. Interaction studies with these agents have only been performed in adults.

As a fixed combination, efavirenz/emtricitabine/tenofovir disoproxil should not be administered concomitantly with other medicinal products containing the components, emtricitabine or tenofovir disoproxil. Efavirenz/emtricitabine/tenofovir disoproxil 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 should not be administered concomitantly with other cytidine analogues, such as lamivudine. Efavirenz/emtricitabine/tenofovir disoproxil should not be administered concomitantly with adefovir dipivoxil or with medicinal products containing tenofovir alafenamide.

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).

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.

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.

Contraindications of concomitant use

Efavirenz/emtricitabine/tenofovir disoproxil must not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, triazolam, pimozide, bepridil, or ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine), since inhibition of their metabolism may lead to serious, life-threatening events (see section 4.3).

Elbasvir/grazoprevir
Co-administration of efavirenz/emtricitabine/tenofovir disoproxil with elbasvir/grazoprevir is contraindicated because it may lead to loss of virologic response to elbasvir/grazoprevir (see section 4.3 and Table 1).

Voriconazole
Co-administration of standard doses of efavirenz and voriconazole is contraindicated. Since efavirenz/emtricitabine/tenofovir disoproxil is a fixed-dose combination product, the dose of efavirenz cannot be altered; therefore, voriconazole and efavirenz/emtricitabine/tenofovir disoproxil must not be co-administered (see section 4.3 and Table 1).

St. John's wort (Hypericum perforatum)
Co-administration of efavirenz/emtricitabine/tenofovir disoproxil and St. John's wort or herbal preparations containing St. John's wort is contraindicated. Plasma levels of efavirenz can be reduced

by concomitant use of St. John's wort due to induction of active substance metabolising enzymes and/or transport proteins by St. John's wort. If a patient is already taking St. John's wort, stop St. John's wort, check viral levels and if possible efavirenz levels. Efavirenz levels may increase on stopping St. John's wort. The inducing effect of St. John's wort may persist for at least 2 weeks after cessation of treatment (see section 4.3).

Metamizole
Co-administration of efavirenz with metamizole, which is an inducer of metabolising enzymes including CYP2B6 and CYP3A4 may cause a reduction in plasma concentrations of efavirenz with potential decrease in clinical efficacy. Therefore, caution is advised when metamizole and efavirenz are administered concurrently; clinical response and/or active substance levels should be monitored as appropriate.

QT Prolonging medicinal products
Efavirenz/emtricitabine/tenofovir disoproxil is contraindicated with concomitant use of medicinal products that are known to prolong the QTc interval and could lead to Torsade de Pointes, such as: antiarrhythmics of classes IA and III, neuroleptics and antidepressant agents, certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole, and triazole antifungal agents, certain non-sedating antihistaminics (terfenadine, astemizole), cisapride, flecainide, certain antimalarials and methadone (see section 4.3).

Concomitant use not recommended

Atazanavir/ritonavir
Insufficient data are available to make a dosing recommendation for atazanavir/ritonavir in combination with efavirenz/emtricitabine/tenofovir disoproxil. Therefore co-administration of atazanavir/ritonavir and efavirenz/emtricitabine/tenofovir disoproxil is not recommended (see Table 1).

Didanosine
Co-administration of efavirenz/emtricitabine/tenofovir disoproxil and didanosine is not recommended (see Table 1).

Sofosbuvir/velpatasvir and sofosbuvir/velpatasvir/voxilaprevir
Co-administration of efavirenz/emtricitabine/tenofovir disoproxil and sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir is not recommended (see section 4.4 and Table 1).

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

Use of efavirenz/emtricitabine/tenofovir disoproxil should be avoided with concurrent or recent use of a nephrotoxic medicinal product. Some examples include, but are not limited to, aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2 (see section 4.4).

Praziquantel
Concomitant use with praziquantel is not recommended due to significant decrease in plasma concentrations of praziquantel, with risk of treatment failure due to increased hepatic metabolism by efavirenz. In case the combination is needed, an increased dose of praziquantel could be considered.

Other interactions

Interactions between efavirenz/emtricitabine/tenofovir disoproxil or its individual component(s) and

other medicinal products are listed in Table 1 below (increase is indicated as "↑", decrease as "↓", no change as "↔", twice daily as "b.i.d.", once daily as "q.d." and once every 8 hours as "q8h"). If available, 90% confidence intervals are shown in parentheses.

Table 1: Interactions between efavirenz/emtricitabine/tenofovir disoproxil or its individual components and other medicinal products

Medicinal product by therapeutic areas	**Effects on active substances levels Mean percent change in AUC, C_{max}, C_{min} with 90% confidence intervals if available (mechanism)**	**Recommendation concerning co-administration with efavirenz/emtricitabine/tenofovir disoproxil (efavirenz 600 mg, emtricitabine 200 mg, tenofovir disoproxil 245 mg)**
ANTI-INFECTIVES		
HIV antivirals		
Protease inhibitors		
Atazanavir/ritonavir/Tenofovir disoproxil (300 mg q.d./100 mg q.d./245 mg q.d.)	Atazanavir: AUC: ↓ 25% (↓ 42 to ↓ 3) C_{max}: ↓ 28% (↓ 50 to ↑ 5) C_{min}: ↓ 26% (↓ 46 to ↑ 10) Co-administration of atazanavir/ritonavir with tenofovir 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 a is not recommended.
Atazanavir/ritonavir/Efavirenz (400 mg q.d./100 mg q.d./600 mg q.d., all administered with food) Atazanavir/ritonavir/Efavirenz (400 mg q.d./200 mg q.d./600 mg q.d., all administered with food)	Atazanavir (pm): AUC: ↔* (↓ 9% to ↑ 10%) C_{max}: ↑ 17%* (↑ 8 to ↑ 27) C_{min}: ↓ 42%* (↓ 31 to ↓ 51) Atazanavir (pm): AUC: ↔*/** (↓ 10% to ↑ 26%) C_{max}: ↔*/** (↓ 5% to ↑ 26%) C_{min}: ↑ 12%*/** (↓ 16 to ↑ 49) (CYP3A4 induction). * When compared to atazanavir 300 mg/ritonavir 100 mg q.d. in the evening without efavirenz. This decrease in atazanavir Cmin might negatively impact the efficacy of atazanavir. ** based on historical comparison. Co-administration of efavirenz with atazanavir/ritonavir is not recommended.	
Atazanavir/ritonavir/Emtricitabine	Interaction not studied.	
Darunavir/ritonavir/Efavirenz (300 mg b.i.d.*/100 mg b.i.d./600 mg q.d.) *lower than recommended doses; similar findings are expected with recommended doses.	Darunavir: AUC: ↓ 13% C_{min}: ↓ 31% C_{max}: ↓ 15% (CYP3A4 induction) Efavirenz: AUC: ↑ 21% C_{min}: ↑ 17% C_{max}: ↑ 15% (CYP3A4 inhibition)	Efavirenz/emtricitabine/tenofovir disoproxil in combination with darunavir/ritonavir 800/100 mg once daily may result in suboptimal darunavir C_{min}. If efavirenz/emtricitabine/tenofovir disoproxil is to be used in combination with darunavir/ritonavir, the darunavir/ritonavir 600/100 mg twice daily regimen should be used. Darunavir/ritonavir should
Darunavir/ritonavir/Tenofovir disoproxil (300 mg b.i.d.*/100 mg	Darunavir: AUC: ↔ C_{min}: ↔	

b.i.d./245 mg q.d.) *lower than recommended dose	 Tenofovir: AUC: ↑ 22% C_{min}: ↑ 37%	be used with caution in combination with efavirenz/emtricitabine/tenofovir disoproxil. See ritonavir row below. Monitoring of renal function may be indicated, particularly in patients with underlying systemic or renal disease, or in patients taking nephrotoxic agents.
Darunavir/ritonavir/Emtricitabine	Interaction not studied. Based on the different elimination pathways, no interaction is expected.	
Fosamprenavir/ritonavir/Efavirenz (700 mg b.i.d./100 mg b.i.d./600 mg q.d.)	No clinically significant pharmacokinetic interaction.	Efavirenz/emtricitabine/tenofovir disoproxil and fosamprenavir/ritonavir can be co-administered without dose adjustment. See ritonavir row below.
Fosamprenavir/ritonavir/Emtricitabine	Interaction not studied.	
Fosamprenavir/ritonavir/Tenofovir disoproxil	Interaction not studied.	
Indinavir/Efavirenz (800 mg q8h/200 mg q.d.)	Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Indinavir: AUC: ↓ 31% (↓ 8 to ↓ 47) C_{min}: ↓ 40% A similar reduction in indinavir exposures was observed when indinavir 1 000 mg q8h was given with efavirenz 600 mg q.d. (CYP3A4 induction) For co-administration of efavirenz with low-dose ritonavir in combination with a protease inhibitor, see section on ritonavir below.	Insufficient data are available to make a dosing recommendation for indinavir when dosed with efavirenz/emtricitabine/tenofovir disoproxil. While the clinical significance of decreased indinavir concentrations has not been established, the magnitude of the observed pharmacokinetic interaction should be taken into consideration when choosing a regimen containing both efavirenz, a component of efavirenz/emtricitabine/tenofovir disoproxil, and indinavir.
Indinavir/Emtricitabine (800 mg q8h/200 mg q.d.)	Indinavir: AUC: ↔ C_{max}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔	
Indinavir/Tenofovir disoproxil (800 mg q8h/245 mg q.d.)	Indinavir: AUC: ↔ C_{max}: ↔ Tenofovir: AUC: ↔ C_{max}: ↔	
Lopinavir/ritonavir/Tenofovir disoproxil (400 mg b.i.d./100 mg b.i.d./245 mg q.d.)	Lopinavir/Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 32% (↑ 25 to ↑ 38)	Insufficient data are available to make a dosing recommendation for lopinavir/ritonavir when dosed with efavirenz/emtricitabine/tenofovir disoproxil. Co-administration of lopinavir/ritonavir and

	C_{max}: ↔ C_{min}: ↑ 51% (↑ 37 to ↑ 66) Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders.	efavirenz/emtricitabine/tenofovir disoproxil is not recommended.
Lopinavir/ritonavir soft capsules or oral solution/Efavirenz Lopinavir/ritonavir tablets/Efavirenz (400/100 mg b.i.d./600 mg q.d.) (500/125 mg b.i.d./600 mg q.d.)	Substantial decrease in lopinavir exposure, necessitating dose adjustment of lopinavir/ritonavir. When used in combination with efavirenz and two nucleoside reverse transcriptase inhibitors (NRTIs), 533/133 mg lopinavir/ritonavir (soft capsules) twice daily yielded similar lopinavir plasma concentrations as compared to lopinavir/ritonavir (soft capsules) 400/100 mg twice daily without efavirenz (historical data). Lopinavir concentrations: ↓ 30-40% Lopinavir concentrations: similar to lopinavir/ritonavir 400/100 mg twice daily without efavirenz. Dose adjustment of lopinavir/ritonavir is necessary when given with efavirenz. For co-administration of efavirenz with low-dose ritonavir in combination with a protease inhibitor, see section on ritonavir below.	
Lopinavir/ritonavir/Emtricitabine	Interaction not studied.	
Ritonavir/Efavirenz (500 mg b.i.d./600 mg q.d.)	Ritonavir: Morning AUC: ↑ 18% (↑ 6 to ↑ 33) Evening AUC: ↔ Morning C_{max}: ↑ 24% (↑ 12 to ↑ 38) Evening C_{max}: ↔ Morning C_{min}: ↑ 42% (↑ 9 to ↑ 86) Evening C_{min}: ↑ 24% (↑ 3 to ↑ 50) Efavirenz: AUC: ↑ 21% (↑ 10 to ↑ 34) C_{max}: ↑ 14% (↑ 4 to ↑ 26) C_{min}: ↑ 25% (↑ 7 to ↑ 46) (inhibition of CYP-mediated oxidative metabolism) When efavirenz was given with ritonavir 500 mg or 600 mg twice daily, the combination was not well tolerated (for example, dizziness, nausea, paraesthesia and elevated liver enzymes occurred). Sufficient data on the tolerability of efavirenz with low-dose ritonavir (100 mg, once or twice daily) are not available.	Co-administration of ritonavir at doses of 600 mg and efavirenz/emtricitabine/tenofovir disoproxil is not recommended. When using efavirenz/emtricitabine/tenofovir disoproxil 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.
Ritonavir/Emtricitabine	Interaction not studied.	
Ritonavir/Tenofovir disoproxil	Interaction not studied.	

Saquinavir/ritonavir/Efavirenz	Interaction not studied. For co-administration of efavirenz with low-dose ritonavir in combination with a protease inhibitor, see section on ritonavir above.	Insufficient data are available to make a dosing recommendation for saquinavir/ritonavir when dosed with efavirenz/emtricitabine/tenofovir disoproxil. Co-administration of saquinavir/ritonavir and efavirenz/emtricitabine/tenofovir disoproxil is not recommended. Use of efavirenz/emtricitabine/tenofovir disoproxil in combination with saquinavir as the sole protease inhibitor is not recommended.
Saquinavir/ritonavir/Tenofovir disoproxil	There were no clinically significant pharmacokinetic interactions when tenofovir disoproxil was co-administered with ritonavir boosted saquinavir.	
Saquinavir/ritonavir/Emtricitabine	Interaction not studied.	
CCR5 antagonist		
Maraviroc/Efavirenz (100 mg b.i.d./600 mg q.d.)	Maraviroc: AUC12h: ↓ 45% (↓ 38 to ↓ 51) C_{max}: ↓ 51% (↓ 37 to ↓ 62) Efavirenz concentrations not measured, no effect is expected.	Refer to the Summary of Product Characteristics for the medicinal product containing maraviroc.
Maraviroc/Tenofovir disoproxil (300 mg b.i.d./245 mg q.d.)	Maraviroc: AUC_{12h}: ↔ C_{max}: ↔ Tenofovir concentrations not measured, no effect is expected.	
Maraviroc/Emtricitabine	Interaction not studied.	
Integrase strand transfer inhibitor		
Raltegravir/Efavirenz (400 mg single dose/-)	Raltegravir: AUC: ↓ 36% C_{12h}: ↓ 21% C_{max}: ↓ 36% (UGT1A1 induction)	Efavirenz/emtricitabine/tenofovir disoproxil and raltegravir can be co-administered without dose adjustment.
Raltegravir/Tenofovir disoproxil (400 mg b.i.d./-)	Raltegravir: AUC: ↑ 49% C_{12h}: ↑ 3% C_{max}: ↑ 64% (mechanism of interaction unknown) Tenofovir: AUC: ↓ 10% C_{12h}: ↓ 13% C_{max}: ↓ 23%	
Raltegravir/Emtricitabine	Interaction not studied.	
NRTIs and NNRTIs		
NRTIs/Efavirenz	Specific interaction studies have not been performed with efavirenz and NRTIs other than lamivudine, zidovudine and tenofovir disoproxil. Clinically significant interactions have not been found and would not be expected since the NRTIs are metabolised via a different route than efavirenz and would be unlikely to compete for the same metabolic enzymes and elimination	Due to the similarity between lamivudine and emtricitabine, a component of efavirenz/emtricitabine/tenofovir disoproxil, efavirenz/emtricitabine/tenofovir disoproxil should not be administered concomitantly with lamivudine (see section 4.4).

	pathways.	
NNRTIs/Efavirenz	Interaction not studied.	Since use of two NNRTIs proved not beneficial in terms of efficacy and safety, co-administration of efavirenz/emtricitabine/tenofovir disoproxil and another NNRTI is not recommended.
Didanosine/Tenofovir disoproxil	Co-administration of tenofovir disoproxil and didanosine results in a 40-60% increase in systemic exposure to didanosine.	Co-administration of efavirenz/emtricitabine/tenofovir disoproxil and didanosine is not recommended. Increased systemic exposure to didanosine may increase didanosine related adverse reactions. Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported. Co-administration of tenofovir disoproxil and didanosine at a dose of 400 mg daily has been associated with a significant decrease in CD4 cell count, possibly due to an intracellular interaction increasing phosphorylated (i.e. active) didanosine. A decreased dose of 250 mg didanosine co-administered with tenofovir disoproxil therapy has been associated with reports of high rates of virologic failure within several tested combinations for the treatment of HIV-1 infection.
Didanosine/Efavirenz	Interaction not studied	
Didanosine/Emtricitabine	Interaction not studied	
Hepatitis C antivirals		
Elbasvir/Grazoprevir + Efavirenz	Elbasvir: AUC: ↓ 54% C_{max}: ↓ 45% (CYP3A4 or P-gp induction - effect on elbasvir) Grazoprevir: AUC: ↓ 83% C_{max}: ↓ 87% (CYP3A4 or P-gp induction - effect on grazoprevir) Efavirenz: AUC: ↔ C_{max}: ↔	Co-administration of efavirenz/emtricitabine/tenofovir disoproxil with elbasvir/grazoprevir is contraindicated because it may lead to loss of virologic response to elbasvir/grazoprevir. This loss is due to significant decreases in elbasvir/grazoprevir plasma concentrations caused by CYP3A4 or P-gp induction. Refer to the Summary of Product Characteristics for elbasvir/grazoprevir for more information.
Glecaprevir/Pibrentasvir/Efavirenz	*Expected:* Glecaprevir: ↓ Pibrentasvir: ↓	Concomitant administration of glecaprevir/pibrentasvir with efavirenz, a component of efavirenz/emtricitabine/tenofovir disoproxil, may significantly

		decrease plasma concentrations of glecaprevir and pibrentasvir, leading to reduced therapeutic effect. Co-administration of glecaprevir/pibrentasvir with efavirenz/emtricitabine/tenofovir disoproxil is not recommended. Refer to the prescribing information for glecaprevir/pibrentasvir for more information.
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Efavirenz/Emtricitabine/Tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)	Ledipasvir: AUC: ↓ 34% (↓ 41 to ↓ 25) C_{max}: ↓ 34% (↓ 41 to ↑ 25) C_{min}: ↓ 34% (↓ 43 to ↑ 24) Sofosbuvir: AUC: ↔ C_{max}: ↔ GS331007[1]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 98% (↑ 77 to ↑ 123) C_{max}: ↑ 79% (↑ 56 to ↑ 104) C_{min}: ↑ 163% (↑ 137 to ↑ 197)	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4).
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Efavirenz/Emtricitabine/Tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ C_{max}: ↑ 38% (↑ 14 to ↑ 67) GS-331007[1]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Velpatasvir: AUC: ↓ 53% (↓ 61 to ↓ 43) C_{max}: ↓ 47% (↓ 57 to ↓ 36) C_{min}: ↓ 57% (↓ 64 to ↓ 48) Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔	Concomitant administration of efavirenz/emtricitabine/tenofovir disoproxil and sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/ voxilaprevir is expected to decrease plasma concentrations of velpatasvir and voxilaprevir. Co-administration of efavirenz/emtricitabine/tenofovir disoproxil with sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/ voxilaprevir is not recommended (see section 4.4).

	C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 81% (↑ 68 to ↑ 94) C_{max}: ↑ 77% (↑ 53 to ↑ 104) C_{min}: ↑ 121% (↑ 100 to ↑ 143)	
Sofosbuvir/Velpatasvir/Voxilaprevir (400 mg/100 mg/100 mg q.d.) + Efavirenz/Emtricitabine/Tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)	Interaction only studied with sofosbuvir/velpatasvir. *Expected:* Voxilaprevir:↓	
Sofosbuvir (400 mg q.d.) + Efavirenz/Emtricitabine/Tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ C_{max}: ↓ 19% (↓ 40 to ↑ 10) GS331007[1]: AUC: ↔ C_{max}: ↓ 23% (↓ 30 to ↑ 16) Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↑ 25% (↑ 8 to ↑ 45) C_{min}: ↔	Efavirenz/emtricitabine/tenofovir disoproxil and sofosbuvir can be coadministered without dose adjustment
Antibiotics		
Clarithromycin/Efavirenz (500 mg b.i.d./400 mg q.d.)	Clarithromycin: AUC: ↓ 39% (↓ 30 to ↓ 46) C_{max}: ↓ 26% (↓ 15 to ↓ 35) Clarithromycin 14-hydroxymetabolite: AUC: ↑ 34% (↑ 18 to ↑ 53) C_{max}: ↑ 49% (↑ 32 to ↑ 69) Efavirenz: AUC: ↔ C_{max}: ↑ 11% (↑ 3 to ↑ 19) (CYP3A4 induction) Rash developed in 46% of uninfected volunteers receiving efavirenz and clarithromycin.	The clinical significance of these changes in clarithromycin plasma levels is not known. Alternatives to clarithromycin (e.g. azithromycin) may be considered. Other macrolide antibiotics, such as erythromycin, have not been studied in combination with efavirenz/emtricitabine/tenofovir disoproxil.
Clarithromycin/Emtricitabine	Interaction not studied.	
Clarithromycin/Tenofovir disoproxil	Interaction not studied.	
Antimycobacterials		

Rifabutin/Efavirenz (300 mg q.d./600 mg q.d.)	Rifabutin: AUC: ↓ 38% (↓ 28 to ↓ 47) C_{max}: ↓ 32% (↓ 15 to ↓ 46) C_{min}: ↓ 45% (↓ 31 to ↓ 56) Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↓ 12% (↓ 24 to ↑ 1) (CYP3A4 induction)	The daily dose of rifabutin should be increased by 50% when given with efavirenz/emtricitabine/tenofovir disoproxil. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week in combination with efavirenz/emtricitabine/tenofovir disoproxil. The clinical effect of this dose adjustment has not been adequately evaluated. Individual tolerability and virological response should be considered when making the dose adjustment (see section 5.2).
Rifabutin/Emtricitabine	Interaction not studied.	
Rifabutin/Tenofovir disoproxil	Interaction not studied.	
Rifampicin/Efavirenz (600 mg q.d./600 mg q.d.)	Efavirenz: AUC: ↓ 26% (↓ 15 to ↓ 36) C_{max}: ↓ 20% (↓ 11 to ↓ 28) C_{min}: ↓ 32% (↓ 15 to ↓ 46) (CYP3A4 and CYP2B6 induction)	When efavirenz/emtricitabine/tenofovir disoproxil is taken with rifampicin in patients weighing 50 kg or greater, an additional 200 mg/day (800 mg total) of efavirenz may provide exposure similar to a daily efavirenz dose of 600 mg when taken without rifampicin. The clinical effect of this dose adjustment has not been adequately evaluated. Individual tolerability and virological response should be considered when making the dose adjustment (see section 5.2). No dose adjustment of rifampicin is recommended when given with efavirenz/emtricitabine/tenofovir disoproxil.
Rifampicin/Tenofovir disoproxil (600 mg q.d./245 mg q.d.)	Rifampicin: AUC: ↔ C_{max}: ↔ Tenofovir: AUC: ↔ C_{max}: ↔	
Rifampicin/Emtricitabine	Interaction not studied.	
Antifungals		
Itraconazole/Efavirenz (200 mg b.i.d./600 mg q.d.)	Itraconazole: AUC: ↓ 39% (↓ 21 to ↓ 53) C_{max}: ↓ 37% (↓ 20 to ↓ 51) C_{min}: ↓ 44% (↓ 27 to ↓ 58) (decrease in itraconazole concentrations: CYP3A4 induction) Hydroxyitraconazole: AUC: ↓ 37% (↓ 14 to ↓ 55) C_{max}: ↓ 35% (↓ 12 to ↓ 52) C_{min}: ↓ 43% (↓ 18 to ↓ 60) Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔	Since no dose recommendation can be made for itraconazole when used with efavirenz/emtricitabine/tenofovir disoproxil, an alternative antifungal treatment should be considered.
Itraconazole/Emtricitabine	Interaction not studied.	
Itraconazole/Tenofovir disoproxil	Interaction not studied.	

Posaconazole/Efavirenz (-/400 mg q.d.)	Posaconazole: AUC: ↓ 50% C_{max}: ↓ 45% (UDP-G induction)	Concomitant use of posaconazole and efavirenz/emtricitabine/tenofovir disoproxil should be avoided unless the benefit to the patient outweighs the risk.
Posaconazole/Emtricitabine	Interaction not studied.	
Posaconazole/Tenofovir disoproxil	Interaction not studied.	
Voriconazole/Efavirenz (200 mg b.i.d./400 mg q.d.)	Voriconazole: AUC: ↓ 77% C_{max}: ↓ 61% Efavirenz: AUC: ↑ 44% C_{max}: ↑ 38% (competitive inhibition of oxidative metabolism) Co-administration of standard doses of efavirenz and voriconazole is contraindicated (see section 4.3).	Since efavirenz/emtricitabine/tenofovir disoproxil is a fixeddose Combination product, the dose of efavirenz cannot be altered; therefore, voriconazole and efavirenz/emtricitabine/tenofovir disoproxil must not be co-administered.
Voriconazole/Emtricitabine	Interaction not studied.	
Voriconazole/Tenofovir disoproxil	Interaction not studied.	
Antimalarials		
Artemether/Lumefantrine/Efavirenz (20/120 mg tablet, 6 doses of 4 tablets each over 3 days/600 mg q.d.)	Artemether: AUC: ↓ 51% C_{max}: ↓ 21% Dihydroartemisinin (active metabolite): AUC: ↓ 46% C_{max}: ↓ 38% Lumefantrine: AUC: ↓ 21% C_{max}: ↔ Efavirenz: AUC: ↓ 17% C_{max}: ↔ (CYP3A4 induction)	Since decreased concentrations of artemether, dihydroartemisinin, or lumefantrine may result in a decrease of antimalarial efficacy, caution is recommended when efavirenz/emtricitabine/tenofovir disoproxil and artemether/lumefantrine tablets are co-administered.
Artemether/Lumefantrine/Emtricitabine	Interaction not studied.	
Artemether/Lumefantrine/Tenofovir disoproxil	Interaction not studied.	
Atovaquone and proguanil hydrochloride/Efavirenz (250/100 mg single dose/600 mg q.d.)	Atovaquone: AUC: ↓ 75% (↓ 62 to ↓ 84) C_{max}: ↓ 44% (↓ 20 to ↓ 61) Proguanil: AUC: ↓ 43% (↓ 7 to ↓ 65) C_{max}: ↔	Concomitant administration of atovaquone/proguanil with efavirenz/emtricitabine/tenofovir disoproxil should be avoided.
Atovaquone and proguanil hydrochloride/Emtricitabine	Interaction not studied.	
Atovaquone and proguanil hydrochloride/Tenofovir disoproxil	Interaction not studied.	
ANTICONVULSANTS		

Carbamazepine/Efavirenz (400 mg q.d./600 mg q.d.)	Carbamazepine: AUC: ↓ 27% (↓ 20 to ↓ 33) C_{max}: ↓ 20% (↓ 15 to ↓ 24) C_{min}: ↓ 35% (↓ 24 to ↓ 44) Efavirenz: AUC: ↓ 36% (↓ 32 to ↓ 40) C_{max}: ↓ 21% (↓ 15 to ↓ 26) C_{min}: ↓ 47% (↓ 41 to ↓ 53) (decrease in carbamazepine concentrations: CYP3A4 induction; decrease in efavirenz concentrations: CYP3A4 and CYP2B6 induction) Co-administration of higher doses of either efavirenz or carbamazepine has not been studied.	No dose recommendation can be made for the use of efavirenz/emtricitabine/tenofovir disoproxil with carbamazepine. An alternative anticonvulsant should be considered. Carbamazepine plasma levels should be monitored periodically.
Carbamazepine/Emtricitabine	Interaction not studied.	
Carbamazepine/Tenofovir disoproxil	Interaction not studied.	
Phenytoin, Phenobarbital, and other anticonvulsants that are substrates of CYP isozymes	Interaction not studied with efavirenz, emtricitabine, or tenofovir disoproxil. There is a potential for reduction or increase in the plasma concentrations of phenytoin, phenobarbital and other anticonvulsants that are substrates of CYP isozymes with efavirenz.	When efavirenz/emtricitabine/tenofovir disoproxil is coadministered with an anticonvulsant that is a substrate of CYP isozymes, periodic monitoring of anticonvulsant levels should be conducted.
Valproic acid/Efavirenz (250 mg b.i.d./600 mg q.d.)	No clinically significant effect on efavirenz pharmacokinetics. Limited data suggest there is no clinically significant effect on valproic acid pharmacokinetics.	Efavirenz/emtricitabine/tenofovir disoproxil and valproic acid can be co-administered without dose adjustment. Patients should be monitored for seizure control.
Valproic acid/Emtricitabine	Interaction not studied.	
Valproic acid/Tenofovir disoproxil	Interaction not studied.	
Vigabatrin/Efavirenz Gabapentin/Efavirenz	Interaction not studied. Clinically significant interactions are not expected since vigabatrin and gabapentin are exclusively eliminated unchanged in the urine and are unlikely to compete for the same metabolic enzymes and elimination pathways as efavirenz.	Efavirenz/emtricitabine/tenofovir disoproxil and vigabatrin or gabapentin can be coadministered without dose adjustment.
Vigabatrin/Emtricitabine Gabapentin/Emtricitabine	Interaction not studied.	
Vigabatrin/Tenofovir disoproxil Gabapentin/Tenofovir disoproxil	Interaction not studied.	
ANTICOAGULANTS		
Warfarin/Efavirenz Acenocoumarol/Efavirenz	Interaction not studied. Plasma concentrations and effects of warfarin or acenocoumarol are potentially increased or decreased by efavirenz.	Dose adjustment of warfarin or acenocoumarol may be required when co-administered with efavirenz/emtricitabine/tenofovir disoproxil.
ANTIDEPRESSANTS		
Selective Serotonin Reuptake Inhibitors (SSRIs)		
Sertraline/Efavirenz (50 mg q.d./600 mg q.d.)	Sertraline: AUC: ↓ 39% (↓ 27 to ↓ 50)	When co-administered with efavirenz/emtricitabine/tenofovir

	C_{max}: ↓ 29% (↓ 15 to ↓ 40) C_{min}: ↓ 46% (↓ 31 to ↓ 58) Efavirenz: AUC: ↔ C_{max}: ↑ 11% (↑ 6 to ↑ 16) C_{min}: ↔ (CYP3A4 induction)	disoproxil, sertraline dose increases should be guided by clinical response.
Sertraline/Emtricitabine	Interaction not studied.	
Sertraline/Tenofovir disoproxil	Interaction not studied.	
Paroxetine/Efavirenz (20 mg q.d./600 mg q.d.)	Paroxetine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔	Efavirenz/emtricitabine/tenofovir disoproxil and paroxetine can be co-administered without dose adjustment.
Paroxetine/Emtricitabine	Interaction not studied.	
Paroxetine/Tenofovir disoproxil	Interaction not studied.	
Fluoxetine/Efavirenz	Interaction not studied. Since fluoxetine shares a similar metabolic profile with paroxetine, i.e. a strong CYP2D6 inhibitory effect, a similar lack of interaction would be expected for fluoxetine.	Efavirenz/emtricitabine/tenofovir disoproxil and fluoxetine can be co-administered without dose adjustment.
Fluoxetine/Emtricitabine	Interaction not studied.	
Fluoxetine/Tenofovir disoproxil	Interaction not studied.	
Norepinephrine and dopamine reuptake inhibitor		
Bupropion/Efavirenz [150 mg single dose (sustained release)/600 mg q.d.]	Bupropion: AUC: ↓ 55% (↓ 48 to ↓ 62) C_{max}: ↓ 34% (↓ 21 to ↓ 47) Hydroxybupropion: AUC: ↔ C_{max}: ↑ 50% (↑ 20 to ↑ 80) (CYP2B6 induction)	Increases in bupropion dose 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.	
CARDIOVASCULAR AGENTS		
Calcium Channel Blockers		
Diltiazem/Efavirenz (240 mg q.d./600 mg q.d.)	Diltiazem: AUC: ↓ 69% (↓ 55 to ↓ 79) C_{max}: ↓ 60% (↓ 50 to ↓ 68) C_{min}: ↓ 63% (↓ 44 to ↓ 75) Desacetyl diltiazem: AUC: ↓ 75% (↓ 59 to ↓ 84) C_{max}: ↓ 64% (↓ 57 to ↓ 69) C_{min}: ↓ 62% (↓ 44 to ↓ 75) N-monodesmethyl diltiazem: AUC: ↓ 37% (↓ 17 to ↓ 52) C_{max}: ↓ 28% (↓ 7 to ↓ 44) C_{min}: ↓ 37% (↓ 17 to ↓ 52)	Dose adjustments of diltiazem when coadministered with efavirenz/emtricitabine/tenofovir disoproxil should be guided by clinical response (refer to the Summary of Product Characteristics for diltiazem).

	Efavirenz: AUC: ↑ 11% (↑ 5 to ↑ 18) C_{max}: ↑ 16% (↑ 6 to ↑ 26) C_{min}: ↑ 13% (↑ 1 to ↑ 26) (CYP3A4 induction) The increase in efavirenz pharmacokinetic parameters is not considered clinically significant.	
Diltiazem/Emtricitabine	Interaction not studied.	
Diltiazem/Tenofovir disoproxil	Interaction not studied.	
Verapamil, Felodipine, Nifedipine and Nicardipine	Interaction not studied with efavirenz, emtricitabine, or tenofovir disoproxil. When efavirenz is coadministered with a calcium channel blocker that is a substrate of the CYP3A4 enzyme, there is a potential for reduction in the plasma concentrations of the calcium channel blocker.	Dose adjustments of calcium channel blockers when co-administered with efavirenz/emtricitabine/tenofovir disoproxil should be guided by clinical response (refer to the Summary of Product Characteristics for the calcium channel blocker).
LIPID LOWERING MEDICINAL PRODUCTS		
HMG Co-A Reductase Inhibitors		
Atorvastatin/Efavirenz (10 mg q.d./600 mg q.d.)	Atorvastatin: AUC: ↓ 43% (↓ 34 to ↓ 50) C_{max}: ↓ 12% (↓ 1 to ↓ 26) 2-hydroxy atorvastatin: AUC: ↓ 35% (↓ 13 to ↓ 40) C_{max}: ↓ 13% (↓ 0 to ↓ 23) 4-hydroxy atorvastatin: AUC: ↓ 4% (↓ 0 to ↓ 31) C_{max}: ↓ 47% (↓ 9 to ↓ 51) Total active HMG Co-A reductase inhibitors: AUC: ↓ 34% (↓ 21 to ↓ 41) C_{max}: ↓ 20% (↓ 2 to ↓ 26)	Cholesterol levels should be periodically monitored. Dose adjustments of atorvastatin may be required when co-administered with efavirenz/emtricitabine/tenofovir disoproxil (refer to the Summary of Product Characteristics for atorvastatin).
Atorvastatin/Emtricitabine	Interaction not studied.	
Atorvastatin/Tenofovir disoproxil	Interaction not studied.	
Pravastatin/Efavirenz (40 mg q.d./600 mg q.d.)	Pravastatin: AUC: ↓ 40% (↓ 26 to ↓ 57) C_{max}: ↓ 18% (↓ 59 to ↑ 12)	Cholesterol levels should be periodically monitored. Dose adjustments of pravastatin may be required when co-administered with efavirenz/emtricitabine/tenofovir disoproxil (refer to the Summary of Product Characteristics for pravastatin).
Pravastatin/Emtricitabine	Interaction not studied.	
Pravastatin/Tenofovir disoproxil	Interaction not studied.	
Simvastatin/Efavirenz (40 mg q.d./600 mg q.d.)	Simvastatin: AUC: ↓ 69% (↓ 62 to ↓ 73) C_{max}: ↓ 76% (↓ 63 to ↓ 79) Simvastatin acid: AUC: ↓ 58% (↓ 39 to ↓ 68)	Cholesterol levels should be periodically monitored. Dose adjustments of simvastatin may be required when co-administered with efavirenz/emtricitabine/tenofovir

	C_{max}: ↓ 51% (↓ 32 to ↓ 58) Total active HMG Co-A reductase inhibitors: AUC: ↓ 60% (↓ 52 to ↓ 68) C_{max}: ↓ 62% (↓ 55 to ↓ 78) (CYP3A4 induction) Co-administration of efavirenz with atorvastatin, pravastatin, or simvastatin did not affect efavirenz AUC or C_{max} values.	disoproxil (refer to the Summary of Product Characteristics for simvastatin).
Simvastatin/Emtricitabine	Interaction not studied.	
Simvastatin/Tenofovir disoproxil	Interaction not studied.	
Rosuvastatin/Efavirenz	Interaction not studied. Rosuvastatin is largely excreted unchanged via the faeces, therefore interaction with efavirenz is not expected.	Efavirenz/emtricitabine/tenofovir disoproxil and rosuvastatin can be co-administered without dose adjustment.
Rosuvastatin/Emtricitabine	Interaction not studied.	
Rosuvastatin/Tenofovir disoproxil	Interaction not studied.	
HORMONAL CONTRACEPTIVES		
Oral: Ethinyloestradiol+Norgestimate/Efavirenz (0.035 mg+0.25 mg q.d./600 mg q.d.)	Ethinyloestradiol: AUC: ↔ C_{max}: ↔ C_{min}: ↓ 8% (↑ 14 to ↓ 25) Norelgestromin (active metabolite): AUC: ↓ 64% (↓ 62 to ↓ 67) C_{max}: ↓ 46% (↓ 39 to ↓ 52) C_{min}: ↓ 82% (↓ 79 to ↓ 85) Levonorgestrel (active metabolite): AUC: ↓ 83% (↓ 79 to ↓ 87) C_{max}: ↓ 80% (↓ 77 to ↓ 83) C_{min}: ↓ 86% (↓ 80 to ↓ 90) (induction of metabolism) Efavirenz: no clinically significant interaction. The clinical significance of these effects is not known.	A reliable method of barrier contraception must be used in addition to hormonal contraceptives (see section 4.6).
Ethinyloestradiol/Tenofovir disoproxil (-/245 mg q.d.)	Ethinyloestradiol: AUC: ↔ C_{max}: ↔ Tenofovir: AUC: ↔ C_{max}: ↔	
Norgestimate/Ethinyloestradiol/ Emtricitabine	Interaction not studied.	
Injection: Depomedroxyprogesterone acetate (DMPA)/Efavirenz (150 mg IM single dose DMPA)	In a 3-month medicinal product interaction study, no significant differences in MPA pharmacokinetic parameters were found between subjects receiving efavirenz-containing antiretroviral therapy and subjects receiving no antiretroviral therapy.	Because of the limited information available, a reliable method of barrier contraception must be used in addition to hormonal contraceptives (see section 4.6).

	Similar results were found by other investigators, although the MPA plasma levels were more variable in the second study. In both studies, plasma progesterone levels for subjects receiving efavirenz and DMPA remained low consistent with suppression of ovulation.	
DMPA/Tenofovir disoproxil	Interaction not studied.	
DMPA/Emtricitabine	Interaction not studied.	
Implant: Etonogestrel/Efavirenz	Decreased exposure of etonogestrel may be expected (CYP3A4 induction). There have been occasional post-marketing reports of contraceptive failure with etonogestrel in efavirenz-exposed patients.	A reliable method of barrier contraception must be used in addition to hormonal contraceptives (see section 4.6).
Etonogestrel/Tenofovir disoproxil	Interaction not studied.	
Etonogestrel/Emtricitabine	Interaction not studied.	
IMMUNOSUPPRESSANTS		
Immunosuppressants metabolised by CYP3A4 (e.g. cyclosporine, tacrolimus, sirolimus)/Efavirenz	Interaction not studied. ↓ exposure of the immunosuppressant may be expected (CYP3A4 induction). These immunosuppressants are not anticipated to impact exposure of efavirenz.	Dose adjustments of the immunosuppressant may be required. Close monitoring of immunosuppressant concentrations for at least two weeks (until stable concentrations are reached) is recommended when starting or stopping treatment with efavirenz/emtricitabine/tenofovir disoproxil.
Tacrolimus/Emtricitabine/Tenofovir disoproxil (0.1 mg/kg q.d./200 mg/245 mg q.d.)	Tacrolimus: AUC: ↔ C_{max}: ↔ C_{24h}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{24h}: ↔ Tenofovir disoproxil: AUC: ↔ C_{max}: ↔ C_{24h}: ↔	
OPIOIDS		
Methadone/Efavirenz (35-100 mg q.d./600 mg q.d.)	Methadone: AUC: ↓ 52% (↓ 33 to ↓ 66) C_{max}: ↓ 45% (↓ 25 to ↓ 59) (CYP3A4 induction) In a study of HIV infected intravenous medicinal product users, co-administration of efavirenz with methadone resulted in decreased plasma levels of methadone and signs of opiate withdrawal. The methadone dose was increased by a mean of 22% to alleviate withdrawal symptoms.	Concomitant administration with efavirenz/emtricitabine/tenofovir disoproxil should be avoided due to the risk for QTc prolongation (see section 4.3).
Methadone/Tenofovir disoproxil (40-110 mg q.d./245 mg q.d.)	Methadone: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir:	

	AUC: ↔ C_{max}: ↔ C_{min}: ↔	
Methadone/Emtricitabine	Interaction not studied.	
Buprenorphine/naloxone/Efavirenz	Buprenorphine: AUC: ↓ 50% Norbuprenorphine: AUC: ↓ 71% Efavirenz: No clinically significant pharmacokinetic interaction.	Despite the decrease in buprenorphine exposure, no patients exhibited withdrawal symptoms. Dose adjustment of buprenorphine may not be necessary when co-administered with efavirenz/emtricitabine/tenofovir disoproxil.
Buprenorphine/naloxone/Emtricitabine	Interaction not studied.	
Buprenorphine/naloxone/Tenofovir disoproxil	Interaction not studied.	

[1] The predominant circulating metabolite of sofosbuvir.

Studies conducted with other medicinal products

There were no clinically significant pharmacokinetic interactions when efavirenz was administered with azithromycin, cetirizine, fosamprenavir/ritonavir, lorazepam, zidovudine, aluminium/magnesium hydroxide antacids, famotidine or fluconazole. The potential for interactions with efavirenz and other azole antifungals, such as ketoconazole, has not been studied.

There were no clinically significant pharmacokinetic interactions when emtricitabine was administered with stavudine, zidovudine or famciclovir. There were no clinically significant pharmacokinetic interactions when tenofovir disoproxil was co-administered with emtricitabine or ribavirin.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential (see below and section 5.3)

Pregnancy should be avoided in women receiving efavirenz/emtricitabine/tenofovir disoproxil. Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz/emtricitabine/tenofovir disoproxil.

Contraception in males and females

Barrier contraception should always be used in combination with other methods of contraception (for example, oral or other hormonal contraceptives, see section 4.5) while on therapy with efavirenz/emtricitabine/tenofovir disoproxil.
Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of efavirenz/emtricitabine/tenofovir disoproxil is recommended.

Pregnancy

Efavirenz
There have been seven retrospective reports of findings consistent with neural tube defects, including meningomyelocele, all in mothers exposed to efavirenz-containing regimens (excluding any efavirenz-containing fixed-dose combination tablets) in the first trimester. Two additional cases (1 prospective and 1 retrospective) including events consistent with neural tube defects have been reported with the fixed-dose combination tablet containing efavirenz, emtricitabine, and tenofovir disoproxil. A causal relationship of these events to the use of efavirenz has not been established, and the denominator is

unknown. As neural tube defects occur within the first 4 weeks of foetal development (at which time neural tubes are sealed), this potential risk would concern women exposed to efavirenz during the first trimester of pregnancy.

As of July 2013, the Antiretroviral Pregnancy Registry (APR) has received prospective reports of 904 pregnancies with first trimester exposure to efavirenz-containing regimens, resulting in 766 live births. One child was reported to have a neural tube defect, and the frequency and pattern of other birth defects were similar to those seen in children exposed to non-efavirenz-containing regimens, as well as those in HIV negative controls. The incidence of neural tube defects in the general population ranges from 0.5-1 case per 1 000 live births.

Malformations have been observed in foetuses from efavirenz-treated monkeys (see section 5.3).

Emtricitabine and tenofovir disoproxil
A large amount of data on pregnant women (more than 1000 pregnancy outcomes) indicates no malformations or foetal/neonatal toxicity associated with emtricitabine and tenofovir disoproxil. Animal studies on emtricitabine and tenofovir disoproxil do not indicate reproductive toxicity (see section 5.3).

Efavirenz/emtricitabine/tenofovir disoproxil should not be used during pregnancy unless the clinical condition of the woman requires treatment with efavirenz/emtricitabine/tenofovir disoproxil.

Breast-feeding

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. Therefore efavirenz/emtricitabine/tenofovir disoproxil should not be used during breast-feeding.

In order to avoid transmission of HIV to the infant it is recommended that women living with HIV do not breast-feed their infants.

Fertility

No human data on the effect of efavirenz/emtricitabine/tenofovir disoproxil 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 efavirenz/emtricitabine/tenofovir disoproxil (study AI266073) or as the component products (study GS-01-934). Adverse reactions were generally consistent with those seen in previous studies of the individual components. The most frequently reported adverse reactions considered possibly or probably related to efavirenz/emtricitabine/tenofovir disoproxil among patients treated up to 48 weeks in study AI266073 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 uncommon events of 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 (see section 4.4).

Discontinuation of efavirenz/emtricitabine/tenofovir disoproxil 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 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).

Tabulated list of adverse reactions

The adverse reactions from clinical study and post-marketing experience with efavirenz/emtricitabine/tenofovir disoproxil and the individual components of efavirenz/emtricitabine/tenofovir disoproxil in antiretroviral combination therapy are listed in Table 2 below by body system organ class, frequency and the component(s) of efavirenz/emtricitabine/tenofovir disoproxil to which the adverse reactions are attributable. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100) or rare (≥ 1/10 000 to < 1/1 000).

Adverse reactions associated with the use of efavirenz/emtricitabine/tenofovir disoproxil
Treatment-emergent adverse reactions considered possibly or probably related to efavirenz/emtricitabine/tenofovir disoproxil reported in study AI266073 (over 48 weeks; n = 203), which have not been associated with one of the individual components of efavirenz/emtricitabine/tenofovir disoproxil, include:

Common:
- anorexia

Uncommon:
- dry mouth
- incoherent speech
- increased appetite
- libido decreased
- myalgia

Table 2: Adverse reactions associated with efavirenz/emtricitabine/tenofovir disoproxil listed by the component(s) of efavirenz/emtricitabine/tenofovir disoproxil to which the adverse reactions are attributable

	Efavirenz	Emtricitabine	Tenofovir disoproxil
Blood and lymphatic system disorders:			
Common		neutropenia	
Uncommon		anaemia[1]	
Immune system disorders:			
Common		allergic reaction	
Uncommon	hypersensitivity		
Metabolism and nutrition disorders:			

	Efavirenz	Emtricitabine	Tenofovir disoproxil
Very common			hypophosphataemia[2]
Common	hypertriglyceridaemia[3]	hyperglycaemia, hypertriglyceridaemia	
Uncommon	hypercholesterolaemia[3]		hypokalaemia[2]
Rare			lactic acidosis
Psychiatric disorders:			
Common	depression (severe in 1.6%)[3], anxiety[3], abnormal dreams[3], insomnia[3]	abnormal dreams, insomnia	
Uncommon	suicide attempt[3], suicide ideation[3], psychosis[3], mania[3], paranoia[3], hallucination[3], euphoric mood[3], affect lability[3], confusional state[3], aggression[3], catatonia[3]		
Rare	completed suicide[3,4], delusion[3,4], neurosis[3,4]		
Nervous system disorders:			
Very common		headache	dizziness
Common	cerebellar coordination and balance disturbances[3], somnolence (2.0%)[3], headache (5.7%)[3], disturbance in attention (3.6%)[3], dizziness (8.5%)[3]	dizziness	headache
Uncommon	convulsions[3], amnesia[3], thinking abnormal[3], ataxia[3], coordination abnormal[3], agitation[3], tremor		
Eye disorders:			
Uncommon	vision blurred		
Ear and labyrinth disorders:			
Uncommon	tinnitus, vertigo		
Vascular disorders:			
Uncommon	flushing		
Gastrointestinal disorders:			
Very common		diarrhoea, nausea	diarrhoea, vomiting, nausea
Common	diarrhoea, vomiting, abdominal pain, nausea	elevated amylase including elevated pancreatic amylase, elevated serum lipase, vomiting, abdominal pain, dyspepsia	abdominal pain, abdominal distension, flatulence
Uncommon	pancreatitis		pancreatitis
Hepatobiliary disorders:			
Common	elevated aspartate aminotransferase (AST), elevated alanine Aminotransferase (ALT), elevated gamma-glutamyltransferase (GGT)	elevated serum AST and/or elevated serum ALT, hyperbilirubinaemia	Increased transaminases

	Efavirenz	Emtricitabine	Tenofovir disoproxil
Uncommon	hepatitis acute		
Rare	hepatic failure[3,4]		hepatic steatosis, hepatitis
Skin and subcutaneous tissue disorders:			
Very common	rash (moderate-severe, 11.6%, all grades, 18%)[3]		rash
Common	pruritus	vesiculobullous rash, pustular rash, maculopapular rash, rash, pruritus, urticaria, skin discolouration (increased pigmentation)[1]	
Uncommon	Stevens-Johnson syndrome, erythema multiforme[3], severe rash (< 1%)	angioedema[4]	
Rare	photoallergic dermatitis		angioedema
Musculoskeletal and connective tissue disorders:			
Very common		elevated creatine kinase	
Uncommon			rhabdomyolysis[2], muscular weakness[2]
Rare			Osteomalacia (manifested as bone pain and infrequently contributing to fractures)[2,4], myopathy[2]
Renal and urinary disorders:			
Uncommon			increased creatinine, proteinuria, proximal renal tubulopathy including Fanconi syndrome
Rare			renal failure (acute and chronic), acute tubular necrosis, nephritis (including acute interstitial nephritis)[4], nephrogenic diabetes insipidus
Reproductive system and breast disorders:			
Uncommon	gynaecomastia		
General disorders and administration site conditions:			
Very common			asthenia
Common	fatigue	pain, asthenia	

[1] Anaemia was common and skin discolouration (increased pigmentation) was very common when emtricitabine was administered to paediatric patients.

[2] This adverse reaction may occur as a consequence of proximal renal tubulopathy. It is not considered to be causally associated with tenofovir disoproxil in the absence of this condition.

[3] See section 4.8 Description of selected adverse reactions for more details.

[4] This adverse reaction was 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 efavirenz in clinical studies (n = 3 969) or exposed to emtricitabine in randomised controlled clinical studies (n = 1 563) or exposed to tenofovir disoproxil in randomised controlled clinical studies and the expanded access programme (n = 7 319).

Description of selected adverse reactions

Rash
In clinical studies 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 can be reinitiated in patients interrupting therapy because of rash. Use of appropriate antihistamines and/or corticosteroids is recommended when efavirenz/emtricitabine/tenofovir disoproxil is restarted.

Psychiatric symptoms
Patients with a history of psychiatric disorders appear to be at greater risk of serious psychiatric adverse reactions listed in the efavirenz column of Table 2.

Nervous system symptoms
Nervous system symptoms are common with efavirenz, one of the components of efavirenz/emtricitabine/tenofovir disoproxil. In clinical controlled studies of efavirenz, nervous system symptoms of moderate to severe intensity were experienced by 19% (severe 2%) of patients, and 2% of patients discontinued therapy due to such symptoms. They usually begin during the first one or two days of efavirenz therapy and generally resolve after the first two to four weeks. They may occur more frequently when efavirenz/emtricitabine/tenofovir disoproxil is taken concomitantly with meals possibly due to increased efavirenz plasma levels (see section 5.2). Dosing at bedtime seems to improve the tolerability of these symptoms (see section 4.2).

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.

Renal impairment
As efavirenz/emtricitabine/tenofovir disoproxil 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. However, in some patients, declines in creatinine clearance did not completely resolve despite tenofovir disoproxil discontinuation. Patients at risk of renal impairment (such as patients with baseline renal risk factors, advanced HIV disease, or patients receiving concomitant nephrotoxic medicinal products) are at increased risk of experiencing incomplete recovery of renal function despite tenofovir disoproxil discontinuation (see section 4.4).

Lactic acidosis
Cases of lactic acidosis have been reported with tenofovir disoproxil alone or in combination with other antiretrovirals. Patients with predisposing factors such as severe hepatic impairment (CPT, Class C) (see section 4.3), or patients receiving concomitant medicinal products known to induce lactic acidosis are at increased risk of experiencing severe lactic acidosis during tenofovir disoproxil treatment, including fatal outcomes.

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

Immune 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 and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Osteonecrosis

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

Paediatric population

Insufficient safety data are available for children below 18 years of age.
efavirenz/emtricitabine/tenofovir disoproxil is not recommended in this population (see section 4.2).

Other special populations

Elderly
Efavirenz/emtricitabine/tenofovir disoproxil has not been studied in patients over the age of 65. Elderly patients are more likely to have decreased hepatic or renal function, therefore caution should be exercised when treating elderly patients with efavirenz/emtricitabine/tenofovir disoproxil (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 (see sections 4.2, 4.4 and 5.2).

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

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

Reporting of suspected adverse reactions

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 via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
Some patients accidentally taking 600 mg efavirenz 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 section 4.8), and standard supportive treatment applied as necessary.

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

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

dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiviral for systemic use, antivirals for treatment of HIV infections, combinations, ATC code: J05AR06.

Mechanism of action and pharmacodynamic effects

Efavirenz is an NNRTI of HIV-1. Efavirenz non-competitively inhibits HIV-1 reverse transcriptase (RT) and does not significantly inhibit human immunodeficiency virus-2 (HIV-2) RT or cellular deoxyribonucleic acid (DNA) polymerases (α, β, γ, and δ). Emtricitabine is a nucleoside analogue of 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. *In vitro* studies have shown that both emtricitabine and tenofovir can be fully phosphorylated when combined together in cells. Emtricitabine triphosphate and tenofovir diphosphate competitively inhibit HIV-1 reverse transcriptase, resulting in DNA chain termination.

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

Cardiac Electrophysiology

The effect of efavirenz on the QTc interval was evaluated in an open-label, positive and placebo controlled, fixed single sequence 3-period, 3-treatment crossover QT study in 58 healthy subjects enriched for CYP2B6 polymorphisms. The mean C_{max} of efavirenz in subjects with CYP2B6 *6/*6 genotype following the administration of 600 mg daily dose for 14 days was 2.25-fold the mean C_{max} observed in subjects with CYP2B6 *1/*1 genotype. A positive relationship between efavirenz concentration and QTc prolongation was observed. Based on the concentration-QTc relationship, the mean QTc prolongation and its upper bound 90% confidence interval are 8.7 ms and 11.3 ms in subjects with CYP2B6*6/*6 genotype following the administration of 600 mg daily dose for 14 days (see section 4.5).

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

Resistance to efavirenz can be selected *in vitro* and resulted in single or multiple amino acid substitutions in HIV-1 RT, including L100I, V108I, V179D, and Y181C. K103N was the most frequently observed RT substitution in viral isolates from patients who experienced rebound in viral

load during clinical studies of efavirenz. Substitutions at RT positions 98, 100, 101, 108, 138, 188, 190 or 225 were also observed, but at lower frequencies, and often only in combination with K103N. Cross resistance profiles for efavirenz, nevirapine and delavirdine *in vitro* demonstrated that the K103N substitution confers loss of susceptibility to all three NNRTIs.

The potential for cross-resistance between efavirenz and NRTIs is low because of the different binding sites on the target and mechanism of action. The potential for cross-resistance between efavirenz and PIs is low because of the different enzyme targets involved.

Resistance to emtricitabine or tenofovir has been seen *in vitro* and in some HIV-1 infected patients due to the development of an M184V or M184I substitution in RT with emtricitabine or a K65R substitution in RT with tenofovir. Emtricitabine-resistant viruses with the M184V/I mutation were cross-resistant to lamivudine, but retained sensitivity to didanosine, stavudine, tenofovir and zidovudine. The K65R mutation can also be selected by abacavir or didanosine and results in reduced susceptibility to these agents plus lamivudine, emtricitabine and tenofovir. Tenofovir disoproxil should be avoided in patients with HIV-1 harbouring the K65R mutation. Both the K65R and M184V/I mutation remain fully susceptible to efavirenz. In addition, a K70E substitution in HIV-1 RT has been selected by tenofovir and results in low-level reduced susceptibility to abacavir, emtricitabine, lamivudine and tenofovir.

Patients with HIV-1 expressing three or more thymidine analogue associated mutations (TAMs) that included either an M41L or an L210W substitution in RT showed reduced susceptibility to tenofovir disoproxil.

In vivo resistance (antiretroviral-naïve patients)
In a 144-week open-label randomised clinical study (GS 01-934) in antiretroviral-naïve patients, where efavirenz, emtricitabine and tenofovir disoproxil were used as individual formulations (or as efavirenz and the fixed combination of emtricitabine and tenofovir disoproxil from week 96 to 144), genotyping was performed on plasma HIV-1 isolates from all patients with confirmed HIV RNA > 400 copies/ml at week 144 or early study medicinal product discontinuation (see section on Clinical experience). As of week 144:

- The M184V/I mutation developed in 2/19 (10.5%) isolates analysed from patients in the efavirenz + emtricitabine + tenofovir disoproxil group and in 10/29 (34.5%) isolates analysed from the efavirenz + lamivudine/zidovudine group (p-value < 0.05, Fisher's Exact test comparing the emtricitabine + tenofovir disoproxil group to the lamivudine/zidovudine group among all subjects).
- No virus analysed contained the K65R or K70E mutation.
- Genotypic resistance to efavirenz, predominantly the K103N mutation, developed in virus from 13/19 (68%) patients in the efavirenz + emtricitabine + tenofovir disoproxil group and in virus from 21/29 (72%) patients in the efavirenz + lamivudine/zidovudine group. A summary of resistance mutation development is shown in Table 3.

Table 3: Development of resistance in study GS-01-934 through week 144

	Efavirenz+ emtricitabine+ tenofovir disoproxil (N=244)	**Efavirenz+lamivudine/ zidovudine (N=243)**
Resistance analysis by week 144	19	31
On-therapy genotypes	19 (100%)	29 (100%)

Efavirenz resistance[1]	13 (68%)	21 (72%)
K103N	8 (42%)	18* (62%)
K101E	3 (16%)	3 (10%)
G190A/S	2 (10.5%)	4 (14%)
Y188C/H	1 (5%)	2 (7%)
V108I	1 (5%)	1 (3%)
P225H	0	2 (7%)
M184V/I	2 (10.5%)	10* (34.5%)
K65R	0	0
K70E	0	0
TAMs[2]	0	2 (7%)

* p-value < 0.05, Fisher's Exact test comparing efavirenz + emtricitabine + tenofovir disoproxil group to efavirenz + lamivudine/zidovudine group among all patients.

1 Other efavirenz resistance mutations included A98G (n=1), K103E (n=1), V179D (n=1), and M230L (n=1).

2 Thymidine analogue associated mutations included D67N (n=1) and K70R (n=1).

In the open-label extended phase of study GS-01-934, where patients received efavirenz/emtricitabine/tenofovir disoproxil on an empty stomach, 3 additional cases of resistance were seen. All 3 subjects had received a fixed dose combination of lamivudine and zidovudine and efavirenz for 144 weeks and then switched to efavirenz/emtricitabine/tenofovir disoproxil. Two subjects with confirmed virologic rebound developed NNRTI resistance-associated substitutions to efavirenz including K103N, V106V/I/M and Y188Y/C reverse transcriptase substitutions at week 240 (96 weeks on efavirenz/emtricitabine/tenofovir disoproxil) and week 204 (60 weeks on efavirenz/emtricitabine/tenofovir disoproxil). A third subject had pre-existing NNRTI resistance-associated substitutions to efavirenz and the M184V reverse transcriptase resistance-associated substitution to emtricitabine at entry into the efavirenz/emtricitabine/tenofovir disoproxil extension phase and experienced a suboptimal virologic response, and developed K65K/R, S68N and K70K/E NRTI resistance-associated substitutions at week 180 (36 weeks on efavirenz/emtricitabine/tenofovir disoproxil).

Please refer to the Summary of Product Characteristics for the individual components for additional information regarding *in vivo* resistance with these medicinal products.

Clinical efficacy and safety

In a 144-week open-label randomised clinical study (GS-01-934) antiretroviral treatment-naïve HIV-1 infected patients received either a once-daily regimen of efavirenz, emtricitabine and tenofovir disoproxil or a fixed combination of lamivudine and zidovudine administered twice daily and efavirenz once daily (please refer to the Summary of Product Characteristics for emtricitabine/tenofovir disoproxil). Patients who completed 144 weeks of treatment with either treatment arm in study GS-01-934 were given the option to continue in an open-label extended phase of the study with efavirenz/emtricitabine/tenofovir disoproxil on an empty stomach. Data are available from 286 patients who switched to efavirenz/emtricitabine/tenofovir disoproxil: 160 had previously received efavirenz, emtricitabine and tenofovir disoproxil, and 126 had previously received lamivudine/zidovudine and efavirenz. High rates of virologic suppression were maintained by subjects from both initial treatment groups who then received efavirenz/emtricitabine/tenofovir disoproxil in the open-label extended phase of the study. After 96 weeks of efavirenz/emtricitabine/tenofovir disoproxil treatment, HIV-1 RNA plasma concentrations remained < 50 copies/ml in 82% of patients and < 400 copies/ml in 85% of patients (intention to treat analysis (ITT), missing=failure).

Study AI266073 was a 48-week open-label randomised clinical study in HIV infected patients comparing the efficacy of efavirenz/emtricitabine/tenofovir disoproxil to antiretroviral therapy consisting of at least two nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) with a protease inhibitor or non-nucleoside reverse transcriptase inhibitor; however not a regimen containing

all efavirenz/emtricitabine/tenofovir disoproxil components (efavirenz, emtricitabine and tenofovir disoproxil). Efavirenz/emtricitabine/tenofovir disoproxil was administered on an empty stomach (see section 4.2). Patients had never experienced virological failure on a previous antiretroviral therapy, had no known HIV-1 mutations that confer resistance to any of the three components within efavirenz/emtricitabine/tenofovir disoproxil, and had been virologically suppressed for at least three months at baseline. Patients either changed to efavirenz/emtricitabine/tenofovir disoproxil (N=203) or continued on their original antiretroviral treatment regimen (N=97). Forty-eight week data showed that high levels of virologic suppression, comparable to the original treatment regimen, were maintained in patients who were randomised to change to efavirenz/emtricitabine/tenofovir disoproxil (see Table 4).

Table 4: 48-week efficacy data from study AI266073 in which efavirenz/emtricitabine/tenofovir disoproxil was administered to virologically suppressed patients on combination antiretroviral therapy

Endpoint	Treatment group		
	Efavirenz/emtricitabine/tenofovir disoproxil (N=203) n/N (%)	Stayed on original treatment regimen (N=97)	Difference between efavirenz/emtricitabine/tenofovir disoproxil and original treatment regimen (95%CI)
	patients with HIV-1 RNA < 50 copies/ml		
PVR (KM)	94.5%	85.5%	8.9% (-7.7% to 25.6%)
M=Excluded	179/181 (98.9%)	85/87 (97.7%)	1.2% (-2.3% to 6.7%)
M=Failure	179/203 (88.2%)	85/97 (87.6%)	0.5% (-7.0% to 9.3%)
Modified LOCF	190/203 (93.6%)	94/97 (96.9%)	-3.3 (-8.3% to 2.7%)
	patients with HIV-1 RNA < 200 copies/ml		
PVR (KM)	98.4%	98.9%	-0.5% (-3.2% to 2.2%)
M=Excluded	181/181 (100%)	87/87 (100%)	0% (-2.4% to 4.2%)
M=Failure	181/203 (89.2%)	87/97 (89.7%)	-0.5% (-7.6% to 7.9%)

PVR (KM): Pure virologic response assessed using the Kaplan Meier (KM) method

M: Missing

Modified LOCF: Post-hoc analysis where patients who failed virologically or discontinued for adverse events were treated as failures; for other drop-outs, the LOCF (last observation carried forward) method was applied

When the two strata were analysed separately, response rates in the stratum with prior PI-treatment were numerically lower for patients switched to efavirenz/emtricitabine/tenofovir disoproxil [92.4% versus 94.0% for the PVR (sensitivity analysis) for efavirenz/emtricitabine/tenofovir disoproxil and SBR patients respectively; a difference (95%CI) of -1.6% (-10.0%, 6.7%). In the prior-NNRTI stratum, response rates were 98.9% vs 97.4% for efavirenz/emtricitabine/tenofovir disoproxil and SBR patients respectively; a difference (95%CI) of 1.4% (-4.0%, 6.9%)].

A similar trend was observed in a sub-group analysis of treatment-experienced patients with baseline HIV-1 RNA < 75 copies/ml from a retrospective cohort study (data collected over 20 months, see Table 5).

Table 5: Maintenance of pure virologic response (Kaplan Meier % (Standard Error) [95%CI]) at week 48 for treatment-experienced patients with baseline HIV-1 RNA < 75 copies/ml who had therapy switched to efavirenz/emtricitabine/tenofovir disoproxil according to the type of prior antiretroviral regimen (Kaiser Permanente patient database)

Prior efavirenz/emtricitabine/tenofovir disoproxil components (N=299)	Prior NNRTI-based regimen (N=104)	Prior PI-based regimen (N=34)
98.9% (0.6%) [96.8%, 99.7%]	98.0% (1.4%) [92.3%, 99.5%]	93.4% (4.5%) [76.2%, 98.3%]

No data are currently available from clinical studies with efavirenz/emtricitabine/tenofovir disoproxil in treatment-naïve patients or in heavily pretreated patients. There is no clinical experience with efavirenz/emtricitabine/tenofovir disoproxil in patients who are experiencing virological failure in a first-line antiretroviral treatment regimen or in combination with other antiretroviral agents.

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).

Paediatric population

The safety and efficacy of efavirenz/emtricitabine/tenofovir disoproxil in children under the age of 18 years have not been established.

5.2 Pharmacokinetic properties

The separate pharmaceutical forms of efavirenz, emtricitabine and tenofovir disoproxil were used to determine the pharmacokinetics of efavirenz, emtricitabine and tenofovir disoproxil, administered separately in HIV infected patients. The bioequivalence of one efavirenz/emtricitabine/tenofovir disoproxil film-coated tablet with one efavirenz 600 mg film-coated tablet plus one emtricitabine 200 mg hard capsule plus one tenofovir disoproxil 245 mg film-coated tablet administered together, was established following single dose administration to fasting healthy subjects in study GS-US-177-0105 (see Table 6).

Table 6: Summary of pharmacokinetic data from study GS-US-177-0105

	Efavirenz (n=45)			Emtricitabine (n=45)			Tenofovir disoproxil (n=45)		
Parameters	**Test**	**Reference**	**GMR (%) (90%CI)**	**Test**	**Reference**	**GMR (%) (90%CI)**	**Test**	**Reference**	**GMR (%) (90%CI)**
C_{max} (ng/ml)	2 264.3 (26.8)	2 308.6 (30.3)	98.79 (92.28, 105.76)	2 130.6 (25.3)	2 384.4 (20.4)	88.84 (84.02, 93.94)	325.1 (34.2)	352.9 (29.6)	91.46 (84.64, 98.83)
$AUC_{0\text{-last}}$ (ng·h/ml)	125 623.6 (25.7)	132 795.7 (27.0)	95.84 (90.73, 101.23)	10 682.6 (18.1)	10 874.4 (14.9)	97.98 (94.90, 101.16)	1 948.8 (32.9)	1 969.0 (32.8)	99.29 (91.02, 108.32)
AUC_{inf} (ng·h/ml)	146 074.9 (33.1)	155 518.6 (34.6)	95.87 (89.63, 102.55)	10 854.9 (17.9)	11 054.3 (14.9)	97.96 (94.86, 101.16)	2 314.0 (29.2)	2 319.4 (30.3)	100.45 (93.22, 108.23)
$T_{1/2}$ (h)	180.6 (45.3)	182.5 (38.3)		14.5 (53.8)	14.6 (47.8)		18.9 (20.8)	17.8 (22.6)	

Test: single fixed-dose combination tablet taken under fasted conditions.

Reference: single dose of a 600 mg efavirenz tablet, 200 mg emtricitabine capsule and 245 mg tenofovir disoproxil tablet taken under fasted conditions.

Values for Test and Reference are mean (% coefficient of variation).

GMR=geometric least-squares mean ratio, CI=confidence interval

Absorption

In HIV infected patients, peak efavirenz plasma concentrations were attained by 5 hours and steady-state concentrations reached in 6 to 7 days. In 35 patients receiving efavirenz 600 mg once daily, steady-state peak concentration (C_{max}) was 12.9 ± 3.7 µM (29%) [mean ± standard deviation (S.D.) (coefficient of variation (%CV))], steady-state C_{min} was 5.6 ± 3.2 µM (57%), and AUC was 184 ± 73 µM•h (40%).

Emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1 to 2 hours post-dose. Following multiple dose oral administration of emtricitabine to 20 HIV infected patients, steady-state C_{max} was 1.8 ± 0.7 µg/ml (mean ± S.D.) (39%CV), steady-state C_{min} was 0.09 ± 0.07 µg/ml (80%) and the AUC was 10.0 ± 3.1 µg•h/ml (31%) over a 24 hour dosing interval.

Following oral administration of a single 245 mg dose of tenofovir disoproxil to HIV-1 infected patients in the fasted state, maximum tenofovir concentrations were achieved within one hour and the Cmax and AUC (mean ± S.D.) (%CV) values were 296 ± 90 ng/ml (30%) and 2 287 ± 685 ng•h/ml (30%), respectively. The oral bioavailability of tenofovir from tenofovir disoproxil in fasted patients was approximately 25%.

Effect of food

Efavirenz/emtricitabine/tenofovir disoproxil has not been evaluated in the presence of food.

Administration of efavirenz capsules with a high fat meal increased the mean AUC and C_{max} of efavirenz by 28% and 79%, respectively, compared to administration in a fasted state. Compared to fasted administration, dosing of tenofovir disoproxil and emtricitabine in combination with either a high fat meal or a light meal increased the mean AUC of tenofovir by 43.6% and 40.5%, and C_{max} by 16% and 13.5%, respectively without affecting emtricitabine exposures.

Efavirenz/emtricitabine/tenofovir disoproxil is recommended for administration 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). It is anticipated that tenofovir exposure (AUC) will be approximately 30% lower following administration of efavirenz/emtricitabine/tenofovir disoproxil on an empty stomach as compared to the individual component tenofovir disoproxil when taken with food (see section 5.1).

Distribution

Efavirenz is highly bound (> 99%) to human plasma proteins, predominantly albumin.

In vitro binding of emtricitabine to human plasma proteins is < 4% and independent of concentrations over the range of 0.02 to 200 µg/ml. Following intravenous administration the volume of distribution of emtricitabine was approximately 1.4 l/kg. After oral administration, emtricitabine is widely distributed throughout the body. The mean plasma to blood concentration ratio was approximately 1.0 and the mean semen to plasma concentration ratio was approximately 4.0.

In vitro binding of tenofovir to human plasma or serum protein is < 0.7% and 7.2%, respectively over the tenofovir concentration range 0.01 to 25 µg/ml. Following intravenous administration the volume of distribution of tenofovir was approximately 800 ml/kg. After oral administration, tenofovir is widely distributed throughout the body.

Biotransformation

Studies in humans and *in vitro* studies using human liver microsomes have demonstrated that

efavirenz is principally metabolised by the CYP system to hydroxylated metabolites with subsequent glucuronidation of these hydroxylated metabolites. These metabolites are essentially inactive against HIV-1. The *in vitro* studies suggest that CYP3A4 and CYP2B6 are the major isozymes responsible for efavirenz metabolism and that it inhibits CYP isozymes 2C9, 2C19, and 3A4. In *in vitro* studies efavirenz did not inhibit CYP2E1 and inhibited CYP2D6 and CYP1A2 only at concentrations well above those achieved clinically.

Efavirenz plasma exposure may be increased in patients with homozygous G516T genetic variant of the CYP2B6 isozyme. The clinical implications of such an association are unknown; however, the potential for an increased frequency and severity of efavirenz-associated adverse events cannot be excluded.

Efavirenz has been shown to induce CYP3A4 and CYP2B6, resulting in the induction of its own metabolism, which may be clinically relevant in some patients. In uninfected volunteers, multiple doses of 200 to 400 mg per day for 10 days resulted in a lower than predicted extent of accumulation (22 to 42% lower) and a shorter terminal half-life of 40 to 55 hours (single dose half-life 52 to 76 hours). Efavirenz has also been shown to induce UGT1A1. Exposures of raltegravir (a UGT1A1 substrate) are reduced in the presence of efavirenz (see section 4.5, Table 1). Although *in vitro* data suggest that efavirenz inhibits CYP2C9 and CYP2C19, there have been contradictory reports of both increased and decreased exposures to substrates of these enzymes when co-administered with efavirenz *in vivo*. The net effect of co-administration is not clear.

There is limited metabolism of emtricitabine. The biotransformation of emtricitabine includes oxidation of the thiol moiety to form the 3'-sulphoxide diastereomers (approximately 9% of dose) and conjugation with glucuronic acid to form 2'-O-glucuronide (approximately 4% of dose). *In vitro* studies have determined that neither tenofovir disoproxil nor tenofovir are substrates for the CYP enzymes. Neither emtricitabine nor tenofovir inhibited *in vitro* active substance metabolism mediated by any of the major human CYP isoforms involved in active substance biotransformation. Also, emtricitabine did not inhibit uridine 5' diphosphoglucuronyl transferase, the enzyme responsible for glucuronidation.

Elimination

Efavirenz has a relatively long terminal half-life of at least 52 hours after single doses (see also data from bioequivalence study described above) and 40 to 55 hours after multiple doses. Approximately 14 to 34% of a radiolabelled dose of efavirenz was recovered in the urine and less than 1% of the dose was excreted in urine as unchanged efavirenz.

Following oral administration, the elimination half-life of emtricitabine is approximately 10 hours. 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.

Following oral administration, the elimination half-life of tenofovir is approximately 12 to 18 hours. Tenofovir is primarily excreted by the kidneys by both filtration and an active tubular transport system with approximately 70 to 80% of the dose excreted unchanged in urine following intravenous administration. The apparent clearance of tenofovir averaged approximately 307 ml/min. Renal clearance has been estimated to be 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.

Pharmacokinetics in special populations

Age
Pharmacokinetic studies have not been performed with efavirenz, emtricitabine or tenofovir in elderly

patients (over 65 years of age).

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

Ethnicity
Limited data suggest that Asian and Pacific Island patients may have higher exposure to efavirenz but they do not appear to be less tolerant of efavirenz.

Paediatric population
Pharmacokinetic studies have not been performed with efavirenz/emtricitabine/tenofovir disoproxil in infants and children under 18 years of age (see section 4.2).

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

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

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

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

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

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

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

Hepatic impairment
The pharmacokinetics of efavirenz/emtricitabine/tenofovir disoproxil have not been studied in HIV infected patients with hepatic impairment. Efavirenz/emtricitabine/tenofovir disoproxil should be administered with caution to patients with mild hepatic impairment (see sections 4.3 and 4.4).

Efavirenz/emtricitabine/tenofovir disoproxil must not be used in patients with severe hepatic impairment (see section 4.3) and is not recommended for patients with moderate hepatic impairment.

In a single-dose study of efavirenz, half-life was doubled in the single patient with severe hepatic impairment (Child-Pugh-Turcotte Class C), indicating a potential for a much greater degree of accumulation. A multiple-dose study of efavirenz showed no significant effect on efavirenz pharmacokinetics in patients with mild hepatic impairment (Child-Pugh Turcotte Class A) compared with controls. There were insufficient data to determine whether moderate or severe hepatic impairment (Child-Pugh-Turcotte Class B or C) affects efavirenz pharmacokinetics.

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

A single 245 mg dose of tenofovir disoproxil was administered to non-HIV infected patients with varying degrees of hepatic impairment defined according to CPT classification. Tenofovir pharmacokinetics were not substantially altered in subjects with hepatic impairment suggesting that no dose adjustment of tenofovir disoproxil is required in these subjects.

5.3 Preclinical safety data

Efavirenz

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, microophthalmia 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 unscheduled DNA synthesis (UDS) test in primary rat hepatocytes. However, it was negative in an *in vivo* mouse bone marrow micronucleus assay.

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

Reproductive toxicity studies in rats and rabbits showed no effects on mating, fertility, pregnancy or 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

Tablet core

Microcrystalline cellulose
Hydroxypropylcellulose
Sodium laurilsulfate
Croscarmellose sodium
Ferric oxide red (E172)
Magnesium stearate
Sodium stearyl fumarate

Film coating

Poly(vinyl alcohol)
Macrogol 3350
Titanium dioxide (E171)
Talc
Ferric oxide red (E172)
Ferric oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

Shelf life after first opening is 2 months when stored in original packaging at a temperature not above 25°C.

6.4 Special precautions for storage

Do not store above 30°C.
Keep the bottle tightly closed in order to protect from moisture.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle with a child-resistant tamper evident polypropylene closure with integrated a silica gel desiccant.
Pack sizes: 30 film-coated tablets and 90 (3x30) film-coated tablets (3 bottles of 30 tablets).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1263/001 30 film-coated tablets
EU/1/17/1263/002 90 (3 x 30) film-coated tablets

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8 February 2018
Date of latest renewal: 7 November 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

KRKA, d.d., Novo mesto
Šmarješka cesta 6
8501 Novo mesto
Slovenia

TAD Pharma GmbH
Heinz-Lohmann-Straße 5
27472 Cuxhaven
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Efavirenz/Emtricitabine/Tenofovir disoproxil Krka 600 mg/200 mg/245 mg film-coated tablets

efavirenz/emtricitabine/tenofovir disoproxil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 600 mg of efavirenz, 200 mg of emtricitabine and 245 mg of tenofovir disoproxil (as succinate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

30 film-coated tablets
90 (3 bottles of 30) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Shelf life after first opening is 2 months, if not stored above 25°C.
Date of opening: _____

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1263/001 30 film-coated tablets
EU/1/17/1263/002 90 (3 x 30) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Efavirenz/Emtricitabine/Tenofovir disoproxil Krka

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

LABEL for a bottle

1. NAME OF THE MEDICINAL PRODUCT

Efavirenz/Emtricitabine/Tenofovir disoproxil Krka 600 mg/200 mg/245 mg film-coated tablets

efavirenz/emtricitabine/tenofovir disoproxil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 600 mg of efavirenz, 200 mg of emtricitabine and 245 mg of tenofovir disoproxil (as succinate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Shelf life after first opening is 2 months, if not stored above 25°C.
Date of opening: _____

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Efavirenz/Emtricitabine/Tenofovir disoproxil Krka 600 mg/200 mg/245 mg film-coated tablets
efavirenz/emtricitabine/tenofovir disoproxil (efavirenzum/emtricitabinum/tenofovirum disoproxilum)

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Efavirenz/Emtricitabine/Tenofovir disoproxil Krka is and what it is used for

Efavirenz/Emtricitabine/Tenofovir disoproxil Krka contains three active substances that are used to treat human immunodeficiency virus (HIV) infection:

- Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI)
- Emtricitabine is a nucleoside reverse transcriptase inhibitor (NRTI)
- Tenofovir is a nucleotide reverse transcriptase inhibitor (NtRTI)

Each of these active substances, also known as antiretroviral medicines, work by interfering with an enzyme (reverse transcriptase) that is essential for the virus to multiply.

Efavirenz/Emtricitabine/Tenofovir disoproxil Krka is a treatment for Human Immunodeficiency Virus (HIV) infection in adults aged 18 years and over who have previously been treated with other antiretroviral medicines and have their HIV-1 infection under control for at least three months. Patients must not have experienced failure of a previous HIV therapy.

2. What you need to know before you take Efavirenz/Emtricitabine/Tenofovir disoproxil Krka

Do not take Efavirenz/Emtricitabine/Tenofovir disoproxil Krka

- **if you are allergic** to efavirenz, emtricitabine, tenofovir disoproxil or any of the other ingredients of this medicine (listed in section 6).

- **if you have severe liver disease**.

- **if you have a heart condition, such as an abnormal electrical signal called prolongation of the QT interval that puts you at high risk for severe heart rhythm problems (Torsade de Pointes).**

- if any member of your family (parents, grandparents, brothers or sisters) has died suddenly due

to a heart problem or was born with heart problems.

- if your doctor has told you that you have high or low levels of electrolytes such as potassium or magnesium in your blood.

- **if you are currently taking** any of the following medicines (see also "Other medicines and Efavirenz/Emtricitabine/Tenofovir disoproxil Krka"):
  - **astemizole or terfenadine** (used to treat hay fever or other allergies)
  - **bepridil** (used to treat heart disease)
  - **cisapride** (used to treat heartburn)
  - **elbasvir/grazoprevir** (used to treat hepatitis C)
  - **ergot alkaloids** (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine) (used to treat migraines and cluster headaches)
  - **midazolam or triazolam** (used to help you sleep)
  - **pimozide, imipramine, amitriptyline or clomipramine** (used to treat certain mental conditions)
  - **St. John's wort** (*Hypericum perforatum*) (a herbal preparation used for depression and anxiety)
  - **voriconazole** (used to treat fungal infections)
  - **flecainide, metoprolol** (used to treat irregular heart beat)
  - **certain antibiotics** (macrolides, fluoroquinolones, imidazole)
  - **triazole antifungal agents**
  - **certain antimalarial agents**
  - **methadone** (used to treat opiate addiction)

→ **If you are taking any of these medicines, tell your doctor immediately**. Taking these medicines with Efavirenz/Emtricitabine/Tenofovir disoproxil Krka could cause serious or life-threatening side effects or stop these medicines from working properly.

Warnings and precautions

Talk to your doctor or pharmacist before taking Efavirenz/Emtricitabine/Tenofovir disoproxil Krka.

- This medicine is not a cure for HIV infection. While taking Efavirenz/Emtricitabine/Tenofovir disoproxil Krka you may still develop infections or other illnesses associated with HIV infection.

- You must remain under the care of your doctor while taking Efavirenz/Emtricitabine/Tenofovir disoproxil Krka.

- **Tell your doctor**:

  - **if you are taking other medicines** that contain efavirenz, emtricitabine, tenofovir disoproxil, tenofovir alafenamide, or lamivudine or adefovir dipivoxil. Efavirenz/Emtricitabine/Tenofovir disoproxil Krka should not be taken with any of these medicines.

  - **if you have or have had kidney disease**, or if tests have shown problems with your kidneys. Efavirenz/Emtricitabine/Tenofovir disoproxil Krka is not recommended if you have moderate to severe kidney disease.

    Efavirenz/Emtricitabine/Tenofovir disoproxil Krka may affect your kidneys. Before starting treatment, your doctor may order blood tests to assess kidney function. Your doctor may also order blood tests during treatment to monitor your kidneys.

    Efavirenz/Emtricitabine/Tenofovir disoproxil Krka is not usually taken with other medicines that can damage your kidneys (see *Other medicines and Efavirenz/Emtricitabine/Tenofovir*

disoproxil Krka). If this is unavoidable, your doctor will monitor your kidney function once a week.

- **if you have a heart disorder, such as abnormal electrical signal called prolongation of the QT interval.**

- **if you have a history of mental illness**, including depression, or of substance or alcohol abuse. Tell your doctor immediately if you feel depressed, have suicidal thoughts or have strange thoughts (see section 4, *Possible side effects*).

- **if you have a history of convulsions (fits or seizures)** or if you are being treated with anticonvulsant therapy such as carbamazepine, phenobarbital and phenytoin. If you are taking any of these medicines, your doctor may need to check the level of anticonvulsant medicine in your blood to ensure that it is not affected while taking Efavirenz/Emtricitabine/Tenofovir disoproxil Krka. Your doctor may give you a different anticonvulsant.

- **if you have a history of liver disease, including chronic active hepatitis**. Patients with liver disease including chronic hepatitis B or C, who are treated with combination antiretrovirals, have a higher risk of severe and potentially life-threatening liver problems. Your doctor may conduct blood tests in order to check how well your liver is working or may switch you to another medicine. **If you have severe liver disease, do not take Efavirenz/Emtricitabine/Tenofovir disoproxil Krka** (see earlier in section 2, *Do not take Efavirenz/Emtricitabine/Tenofovir disoproxil Krka*).

  If you have hepatitis B infection, your doctor will carefully consider the best treatment regimen for you. Tenofovir disoproxil and emtricitabine, two of the active substances in Efavirenz/Emtricitabine/Tenofovir disoproxil Krka, show some activity against hepatitis B virus although emtricitabine is not approved for the treatment of hepatitis B infection. Symptoms of your hepatitis may become worse after discontinuation of Efavirenz/Emtricitabine/Tenofovir disoproxil Krka. Your doctor may then conduct blood tests at regular intervals in order to check how well your liver is working (see section 3, *If you stop taking Efavirenz/Emtricitabine/Tenofovir disoproxil Krka)*.

- Independent of a history of liver disease, your doctor will consider regular blood tests to check how your liver is working.

- **if you are over 65**. Insufficient numbers of patients over 65 years of age have been studied. If you are over 65 years of age and are prescribed Efavirenz/Emtricitabine/Tenofovir disoproxil Krka, your doctor will monitor you carefully.

- **Once you start taking Efavirenz/Emtricitabine/Tenofovir disoproxil Krka, look out for**:

  - **signs of dizziness, difficulty sleeping, drowsiness, difficulty concentrating or abnormal dreaming**. These side effects may start in the first 1 or 2 days of treatment and usually go away after the first 2 to 4 weeks.

  - **any signs of skin rash**. Rashes may be caused by Efavirenz/Emtricitabine/Tenofovir disoproxil Krka. If you see any signs of a severe rash with blistering or fever, stop taking Efavirenz/Emtricitabine/Tenofovir disoproxil Krka and tell your doctor at once. If you had a rash while taking another NNRTI, you may be at higher risk of getting a rash with Efavirenz/Emtricitabine/Tenofovir disoproxil Krka.

  - **any signs of inflammation or infection**. In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to improvement in the body's immune response, enabling the body to fight

infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please tell your doctor at once.

In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

- **bone problems**. Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

  Bone problems (manifesting as persistent or worsening bone pain and sometimes resulting in fractures) may also occur due to damage to kidney tubule cells (see section 4, *Possible side effects*). Tell your doctor if you have bone pain or fractures.

  Tenofovir disoproxil may also cause loss of bone mass. The most pronounced bone loss was seen in clinical studies when patients were treated for HIV with tenofovir disoproxil in combination with a boosted protease inhibitor.

  Overall, the effects of tenofovir disoproxil on long term bone health and future fracture risk in adult and paediatric patients are uncertain.

  Tell your doctor if you know you suffer from osteoporosis. Patients with osteoporosis are at a higher risk of fractures.

Children and adolescents

- **Do not give Efavirenz/Emtricitabine/Tenofovir disoproxil Krka to children and adolescents** under 18 years of age. The use of Efavirenz/Emtricitabine/Tenofovir disoproxil Krka in children and adolescents has not been studied.

Other medicines and Efavirenz/Emtricitabine/Tenofovir disoproxil Krka

You must not take Efavirenz/Emtricitabine/Tenofovir disoproxil Krka with certain medicines. These are listed under *Do not take Efavirenz/Emtricitabine/Tenofovir disoproxil Krka*, at the start of section 2. They include some common medicines and some herbal preparations (including St. John's wort) which can cause serious interactions.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Also, Efavirenz/Emtricitabine/Tenofovir disoproxil Krka should not be taken with any other medicines that contain efavirenz (unless recommended by your doctor), emtricitabine, tenofovir disoproxil, tenofovir alafenamide, or lamivudine or adefovir dipivoxil.

Tell your doctor if you are taking other medicines which may damage your kidneys. Some examples include:
- aminoglycosides, vancomycin (medicines for bacterial infections)

- foscarnet, ganciclovir, cidofovir (medicines for viral infections)
- amphotericin B, pentamidine (medicines for fungal infections)
- interleukin-2 (to treat cancer)
- non-steroidal anti-inflammatory drugs (NSAIDs, to relieve bone or muscle pains)

Efavirenz/Emtricitabine/Tenofovir disoproxil Krka may interact with other medicines, including herbal preparations such as Ginkgo biloba extracts. As a result, the amounts of Efavirenz/Emtricitabine/Tenofovir disoproxil Krka or other medicines in your blood may be affected. This may stop your medicines from working properly, or may make any side effects worse. In some cases, your doctor may need to adjust your dose or check your blood levels. **It is important to tell your doctor or pharmacist if you are taking any of the following**:

- **Medicines containing didanosine (for HIV infection)**: Taking Efavirenz/Emtricitabine/Tenofovir disoproxil Krka with other antiviral medicines that contain didanosine can raise the levels of didanosine in your blood and may reduce CD4 cell counts. Inflammation of the pancreas and lactic acidosis (excess lactic acid in the blood), which sometimes caused death, have been reported rarely when medicines containing tenofovir disoproxil and didanosine were taken together. Your doctor will carefully consider whether to treat you with medicines containing tenofovir and didanosine.
- **Other medicines used for HIV infection**: The following protease inhibitors: darunavir, indinavir, lopinavir/ritonavir, ritonavir, or ritonavir boosted atazanavir or saquinavir. Your doctor may consider giving you an alternative medicine or changing the dose of the protease inhibitors. Also, tell your doctor if you are taking maraviroc.
- **Medicines used to treat infection with the hepatitis C virus**: elbasvir/grazoprevir, glecaprevir/pibrentasvir, sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir.
- **Medicines used to lower blood fats (also called statins)**: Atorvastatin, pravastatin, simvastatin. Efavirenz/Emtricitabine/Tenofovir disoproxil Krka can reduce the amount of statins in your blood. Your doctor will check your cholesterol levels and will consider changing the dose of your statin, if needed.
- **Medicines used to treat convulsions/seizures (anticonvulsants)**: Carbamazepine, phenytoin, phenobarbital. Efavirenz/Emtricitabine/Tenofovir disoproxil Krka can reduce the amount of the anticonvulsant in your blood. Carbamazepine can reduce the amount of efavirenz, one of the components of Efavirenz/Emtricitabine/Tenofovir disoproxil Krka, in your blood. Your doctor may need to consider giving you a different anticonvulsant.
- **Medicines used to treat bacterial infections**, including tuberculosis and AIDS-related mycobacterium avium complex: Clarithromycin, rifabutin, rifampicin. Your doctor may need to consider changing your dose or giving you an alternative antibiotic. In addition, your doctor may consider giving you an additional dose of efavirenz to treat your HIV infection.
- **Medicines used to treat fungal infections (antifungals)**: Itraconazole or posaconazole. Efavirenz/Emtricitabine/Tenofovir disoproxil Krka can reduce the amount of itraconazole or posaconazole in your blood. Your doctor may need to consider giving you a different antifungal.
- **Medicines used to treat malaria**: Atovaquone/proguanil or artemether/lumefantrine. Efavirenz/Emtricitabine/Tenofovir disoproxil Krka may reduce the amount of atovaquone/proguanil or artemether/lumefantrine in your blood.
- **Hormonal contraceptive, such as birth control pills, an injected contraceptive (for example, Depo-Provera), or a contraceptive implant (for example, Implanon)**: You must also use a reliable barrier method of contraception (see *Pregnancy and breast-feeding*). Efavirenz/Emtricitabine/Tenofovir disoproxil Krka may make hormonal contraceptives less likely to work. Pregnancies have occurred in women taking efavirenz, a component of Efavirenz/Emtricitabine/Tenofovir disoproxil Krka, while using a contraceptive implant, although it has not been established that the efavirenz therapy caused the contraceptive to fail.
- **Praziquantel**, a medicine used to treat parasitic worm infections.
- **Sertraline**, a medicine used to treat depression, as your doctor may need to change your dose of sertraline.
- **Metamizole,** a medicine used to treat pain and fever.
- **Bupropion**, a medicine used to treat depression or to help you stop smoking, as your doctor may need to change your dose of bupropion.

- **Diltiazem or similar medicines (called calcium channel blockers)**: When you start taking Efavirenz/Emtricitabine/Tenofovir disoproxil Krka, your doctor may need to adjust your dose of the calcium channel blocker.
- **Medicines used to prevent organ transplant rejection (also called immunosuppressants)**, such as cyclosporine, sirolimus or tacrolimus. When you start or stop taking Efavirenz/Emtricitabine/Tenofovir disoproxil Krka your doctor will closely monitor your plasma levels of the immunosuppressant and may need to adjust its dose.
- **Warfarin or acenocoumarol** (medicines used to reduce clotting of the blood): Your doctor may need to adjust your dose of warfarin or acenocoumarol.
- **Ginkgo biloba extracts** (herbal preparation).

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Women should not get pregnant during treatment with Efavirenz/Emtricitabine/Tenofovir disoproxil Krka and for 12 weeks thereafter. Your doctor may require you to take a pregnancy test to ensure you are not pregnant before starting treatment with Efavirenz/Emtricitabine/Tenofovir disoproxil Krka.

If you could get pregnant while receiving Efavirenz/Emtricitabine/Tenofovir disoproxil Krka, you need to use a reliable form of barrier contraception (for example, a condom) with other methods of contraception including oral (pill) or other hormonal contraceptives (for example, implants, injection). Efavirenz, one of the active components of Efavirenz/Emtricitabine/Tenofovir disoproxil Krka, may remain in your blood for a time after therapy is stopped. Therefore, you should continue to use contraceptive measures, as above, for 12 weeks after you stop taking Efavirenz/Emtricitabine/Tenofovir disoproxil Krka.

Tell your doctor immediately if you are pregnant or intend to become pregnant. If you are pregnant, you should take Efavirenz/Emtricitabine/Tenofovir disoproxil Krka only if you and your doctor decide it is clearly needed.

Serious birth defects have been seen in unborn animals and in the babies of women treated with efavirenz during pregnancy.

Ask your doctor or pharmacist for advice before taking any medicine.

If you have taken Efavirenz/Emtricitabine/Tenofovir disoproxil Krka during your pregnancy, your doctor may request regular blood tests and other diagnostic tests to monitor the development of your child. In children whose mothers took NRTIs during pregnancy, the benefit from the protection against HIV outweighed the risk of side effects.

Do not breast-feed during treatment with Efavirenz/Emtricitabine/Tenofovir disoproxil Krka. Both HIV and the ingredients of Efavirenz/Emtricitabine/Tenofovir disoproxil Krka may pass through breast milk and cause serious harm to your baby.

Breast-feeding is not recommended in women who are living with HIV because HIV infection can be passed on to the baby in breast milk.

If you are breast-feeding, or thinking about breast-feeding, you should discuss it with your doctor as soon as possible.

Driving and using machines

Efavirenz/Emtricitabine/Tenofovir disoproxil Krka may cause dizziness, impaired concentration

and drowsiness. If you are affected, do not drive and do not use any tools or machines.

Efavirenz/Emtricitabine/Tenofovir disoproxil Krka contains sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Efavirenz/Emtricitabine/Tenofovir disoproxil Krka

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is:
One tablet taken each day by mouth. Efavirenz/Emtricitabine/Tenofovir disoproxil Krka should be taken on an empty stomach (commonly defined as 1 hour before or 2 hours after a meal) preferably at bedtime. This may make some side effects (for example, dizziness, drowsiness) less troublesome. Swallow Efavirenz/Emtricitabine/Tenofovir disoproxil Krka whole with water.

Efavirenz/Emtricitabine/Tenofovir disoproxil Krka must be taken every day.

If your doctor decides to stop one of the components of Efavirenz/Emtricitabine/Tenofovir disoproxil Krka, you may be given efavirenz, emtricitabine and/or tenofovir disoproxil separately or with other medicines for the treatment of your HIV infection.

If you take more Efavirenz/Emtricitabine/Tenofovir disoproxil Krka than you should

If you accidentally take too many Efavirenz/Emtricitabine/Tenofovir disoproxil Krka tablets you may be at increased risk of experiencing possible side effects with this medicine (see section 4, *Possible side effects*). Contact your doctor or nearest emergency department for advice. Keep the tablet bottle with you so that you can easily describe what you have taken.

If you forget to take Efavirenz/Emtricitabine/Tenofovir disoproxil Krka

It is important not to miss a dose of Efavirenz/Emtricitabine/Tenofovir disoproxil Krka.

If you do miss a dose of Efavirenz/Emtricitabine/Tenofovir disoproxil Krka within 12 hours of when it is usually taken, take it as soon as you can, and then take your next dose at its regular time.

If it is almost time (less than 12 hours) for your next dose anyway, do not take the missed dose. Wait and take the next dose at the regular time. Do not take a double dose to make up for a forgotten tablet.

If you throw up the tablet (within 1 hour after taking Efavirenz/Emtricitabine/Tenofovir disoproxil Krka), you should take another tablet. Do not wait until your next dose is due. You do not need to take another tablet if you were sick more than 1 hour after taking Efavirenz/Emtricitabine/Tenofovir disoproxil Krka.

If you stop taking Efavirenz/Emtricitabine/Tenofovir disoproxil Krka

Don't stop taking Efavirenz/Emtricitabine/Tenofovir disoproxil Krka without talking to your doctor. Stopping Efavirenz/Emtricitabine/Tenofovir disoproxil Krka can seriously affect your response to future treatment. If Efavirenz/Emtricitabine/Tenofovir disoproxil Krka is stopped, speak to your doctor before you restart taking Efavirenz/Emtricitabine/Tenofovir disoproxil Krka tablets. Your doctor may consider giving you the components of Efavirenz/Emtricitabine/Tenofovir disoproxil Krka separately if you are having problems or need your dose adjusted.

When your supply of Efavirenz/Emtricitabine/Tenofovir disoproxil Krka starts to run low, get more from your doctor or pharmacist. This is very important because the amount of virus may start to increase if the medicine is stopped for even a short time. The virus may then become harder to treat.

If you have both HIV infection and hepatitis B, it is especially important not to stop your Efavirenz/Emtricitabine/Tenofovir disoproxil Krka treatment without talking to your doctor first. Some patients have had blood tests or symptoms indicating that their hepatitis has got worse after stopping emtricitabine or tenofovir disoproxil (two of the three components of Efavirenz/Emtricitabine/Tenofovir disoproxil Krka). If Efavirenz/Emtricitabine/Tenofovir disoproxil Krka is stopped your doctor may recommend that you resume hepatitis B treatment. You may require blood tests to check how your liver is working for 4 months after stopping treatment. In some patients with advanced liver disease or cirrhosis, stopping treatment is not recommended as this may lead to worsening of your hepatitis, which may be life-threatening.

→ Tell your doctor immediately about new or unusual symptoms after you stop treatment, particularly symptoms you associate with hepatitis B infection.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Possible serious side effects: tell your doctor immediately

- **Lactic acidosis** (excess lactic acid in the blood) is a rare (may affect up to 1 in every 1 000 patients) but serious side effect that can be fatal. The following side effects may be signs of lactic acidosis:
  - deep rapid breathing
  - drowsiness
  - feeling sick (nausea), being sick (vomiting) and stomach pain.

→ If you think you may have lactic acidosis, contact your doctor immediately.

Other possible serious side effects

The following side effects are **uncommon** (these may affect up to 1 in every 100 patients):

- allergic reaction (hypersensitivity) that may cause severe skin reactions (Stevens-Johnson syndrome, erythema multiforme, see section 2)
- swelling of the face, lips, tongue or throat
- angry behaviour, suicidal thoughts, strange thoughts, paranoia, unable to think clearly, mood being affected, seeing or hearing things that are not really there (hallucinations), suicide attempts, personality change (psychosis), catatonia (a condition in which the patient is rendered motionless and speechless for a period)
- pain in the abdomen (stomach), caused by inflammation of the pancreas
- forgetfulness, confusion, fitting (seizures), incoherent speech, tremor (shaking)
- yellow skin or eyes, itching, or pain in the abdomen (stomach) caused by inflammation of the liver
- damage to kidney tubules

Psychiatric side effects in addition to those listed above include delusions (false beliefs), neurosis. Some patients have committed suicide. These problems tend to occur more often in those who have a history of mental illness. Always notify your doctor immediately if you have these symptoms.

Side effects to the liver: If you are also infected with hepatitis B virus, you may experience a worsening of hepatitis after discontinuation of treatment (see section 3).

The following side effects are rare (these may affect up to 1 in every 1 000 patients):

- liver failure, in some cases leading to death or liver transplant. Most cases occurred in patients who already had liver disease, but there have been a few reports in patients without any existing liver disease
- inflammation of the kidney, passing a lot of urine and feeling thirsty
- back pain caused by kidney problems, including kidney failure. Your doctor may do blood tests to see if your kidneys are working properly
- softening of the bones (with bone pain and sometimes resulting in fractures) which may occur due to damage to the kidney tubule cells
- fatty liver

→ If you think that you may have any of these serious side effects, talk to your doctor.

Most frequent side effects

The following side effects are very common (these may affect more than 1 in 10 patients)

- dizziness, headache, diarrhoea, feeling sick (nausea), being sick (vomiting)
- rashes (including red spots or blotches sometimes with blistering and swelling of the skin), which may be allergic reactions
- feeling weak

Tests may also show:
- decreases in phosphate levels in the blood
- increased levels of creatine kinase in the blood that may result in muscle pain and weakness

Other possible side effects

The following side effects are common (these may affect up to 1 in 10 patients)

- allergic reactions
- disturbances of coordination and balance
- feeling worried or depressed
- difficulty sleeping, abnormal dreams, difficulty concentrating, drowsiness
- pain, stomach pain
- problems with digestion resulting in discomfort after meals, feeling bloated, wind (flatulence)
- loss of appetite
- tiredness
- itching
- changes in skin colour including darkening of the skin in patches often starting on hands and soles of feet

Tests may also show:
- low white blood cell count (a reduced white blood cell count can make you more prone to infection)
- liver and pancreas problems
- increased fatty acids (triglycerides), bilirubin or sugar levels in the blood

The following side effects are uncommon (these may affect up to 1 in every 100 patients):

- breakdown of muscle, muscle pain or weakness
- anaemia (low red blood cell count)
- a feeling of spinning or tilting (vertigo), whistling, ringing or other persistent noise in the ears
- blurred vision
- chills
- breast enlargement in males
- decreased sexual drive
- flushing
- dry mouth
- increased appetite

Tests may also show:
- decreases in potassium in the blood
- increases in creatinine in the blood
- proteins in urine
- increased cholesterol in the blood

The breakdown of muscle, softening of the bones (with bone pain and sometimes resulting in fractures), muscle pain, muscle weakness and decreases in potassium or phosphate in the blood may occur due to damage to kidney tubule cells.

The following side effects are rare (these may affect up to 1 in every 1 000 patients)

- itchy rash to the skin caused by a reaction to sunlight

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Efavirenz/Emtricitabine/Tenofovir disoproxil Krka

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the packaging after EXP. The expiry date refers to the last day of that month.

Do not store above 30°C.

Keep the bottle tightly closed in order to protect from moisture.

Shelf life after first opening is 2 months, if not stored above 25°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Efavirenz/Emtricitabine/Tenofovir disoproxil Krka contains
- The active substances are efavirenz, emtricitabine and tenofovir disoproxil. Each film-coated tablet contains 600 mg of efavirenz, 200 mg of emtricitabine and 245 mg of tenofovir disoproxil

(as succinate).
- The other ingredients are:
  Tablet core: microcrystalline cellulose, hydroxypropylcellulose, sodium laurilsulfate, croscarmellose sodium, ferric oxide red (E172), magnesium stearate, sodium stearyl fumarate.
  Film coating: poly(vinyl alcohol), macrogol 3350, titanium dioxide (E171), talc, ferric oxide red (E172), ferric oxide yellow (E172). See section 2 "Efavirenz/Emtricitabine/Tenofovir disoproxil Krka contains sodium".

What Efavirenz/Emtricitabine/Tenofovir disoproxil Krka looks like and contents of the pack

Efavirenz/Emtricitabine/Tenofovir disoproxil Krka film-coated tablets (tablets) are light orange pink, oval, biconvex, film-coated tablets with bevelled edges. Tablet dimension: 20 x 11 mm.

Efavirenz/Emtricitabine/Tenofovir disoproxil Krka is available in bottles of 30 tablets, with a child-resistant tamper evident closer with integrated a desiccant, which helps to protect your tablets from moisture.
The following pack sizes are available: cartons containing 1 bottle of 30 film-coated tablets or 90 (3 bottles of 30) film-coated tablets.

Not all pack sizes may be marketed.

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Manufacturers
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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.