TEEVIR™ 75054244

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For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

TEEVIR™

Efavirenz , Emtricitabine and Tenofovir Disoproxil Fumarate Tablets IP 600 mg/200 mg/300 mg

Label Claim

Each film coated tablet contains:

Efavirenz IP	600 mg
Emtricitabine IP	200 mg
Tenofovir Disoproxil Fumarate IP	300 mg

Colours: Titanium Dioxide, Iron Oxide Red and Iron Oxide Black

List of Excipients:

Microcrystalline Cellulose, Croscarmellose sodium, Hydroxypropyl cellulose (Klucel - LF), Sodium lauryl sulfate, Magnesium stearate, Lactose monohydrate, film coat { Iron Oxide Black, Iron oxide red, Titanium dioxide, Talc, Polyethylene glycol & Polyvinyl alcohol }

Therapeutic indications

The fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults.

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 the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) prior to initiation of their first antiretroviral treatment regimen.

The demonstration of the benefit of the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) 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 the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg). No data are currently available from clinical studies with the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) in treatment-naïve or in heavily pretreated patients.

No data are available to support the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) and other antiretroviral agents.

Posology and method of administration

Therapy should be initiated by a physician experienced in the management of human immunodeficiency virus (HIV) infection.

Posology

Adults: The recommended dose of the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) is one tablet taken orally once daily.

If a patient misses a dose of the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) within 12 hours of the time it is usually taken, the patient should take the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) as soon as possible and resume their normal dosing schedule. If a patient misses a dose of the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) by more than 12 hours and it is almost time for their 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 the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg), another tablet should be taken. If the patient vomits more than 1 hour after taking the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) they do not need to take another dose.

It is recommended that the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) be taken on an empty stomach since food may increase Efavirenz exposure and may lead to an increase in the frequency of adverse reactions. In order to improve the tolerability to efavirenz with respect to undesirable effects on the nervous system, bedtime dosing is recommended.

It is anticipated that tenofovir exposure will be approximately 35% lower following administration of the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) on an empty stomach as compared to the individual component tenofovir disoproxil fumarate when taken with food. In virologically suppressed patients, the clinical relevance of this reduction can be expected to be limited. Further data on the clinical translation of the decrease in pharmacokinetic exposure is awaited.

Where discontinuation of therapy with one of the components of the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) is indicated or where dose modification is necessary, separate preparations of efavirenz, emtricitabine and tenofovir disoproxil fumarate are available. Please refer to the Summary of Product Characteristics for these medicinal products.

If therapy with the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) is discontinued, consideration should be given to the long half-life of efavirenz 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 the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) is co-administered with rifampicin, an additional 200 mg/day (800 mg total) of efavirenz may be considered.

Special populations

Paediatric population: The fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) is not recommended for use in children below 18 years of age due to lack of data on safety and efficacy.

Elderly: The fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) should be administered with caution to elderly patients.

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

Hepatic impairment: The pharmacokinetics of the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) have not been studied in patients with hepatic impairment. Patients with mild-to-moderate liver disease (Child-Pugh-Turcotte (CPT), Grade A or B) may be treated with the normal recommended dose of the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg). Patients should be monitored carefully for adverse reactions, especially nervous system symptoms related to efavirenz. If the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) is discontinued in patients co-infected with HIV and HBV, these patients should be closely monitored for evidence of exacerbation of hepatitis.

Method of administration

It is recommended that the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) be swallowed whole with water, once daily.

Contraindications

Hypersensitivity to the active substances or to any of the excipients. The fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) must not be used in patients with severe hepatic impairment (CPT Class C). The fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) must not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, triazolam, pimozide, bepridil, or ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine), because competition for cytochrome P450 (CYP) 3A4 by efavirenz could result in inhibition of metabolism and create the potential for serious and/or life-threatening undesirable effects (for example, cardiac arrhythmias, prolonged sedation or respiratory depression). Herbal preparations containing St. John's wort (*Hypericum perforatum*) must not be used while taking the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) due to the risk of decreased plasma concentrations and reduced clinical effects of Efavirenz.

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

Special warnings and precautions for use

Co-administration with other medicinal products: The fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) should not be administered concomitantly with other medicinal products containing any of the same active components, efavirenz, emtricitabine or tenofovir disoproxil fumarate. Due to similarities with emtricitabine, the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) should not be administered concomitantly with other cytidine analogues, such as lamivudine. The fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) should not be administered concomitantly with adefovir dipivoxil.

Lactic acidosis: lactic acidosis, usually associated with hepatic steatosis, has been reported with the use of nucleoside analogues. Early symptoms (symptomatic hyperlactataemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness). Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure or renal failure. Lactic acidosis generally occurred after a few or several months of treatment.
Treatment with nucleoside analogues must be discontinued in the setting of symptomatic hyperlactataemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.
Caution should be exercised when administering nucleoside analogues to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicinal products and alcohol). Co-infection with hepatitis C and treatment with alpha interferon and ribavirin may constitute a special risk.
Patients at increased risk must be followed closely.

Opportunistic infections: Patients receiving the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) 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.

Transmission of HIV: Patients must be advised that antiretroviral therapies, including the fixed-dose combination (Efavirenz 600 mg / Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg, have not been proven to prevent the risk of transmission of HIV to others through sexual contact or contamination with blood. Appropriate precautions must continue to be used.

Liver disease: The pharmacokinetics, safety and efficacy of the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) have not been established in patients with significant underlying liver disorders. The fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) is contraindicated in patients with severe hepatic impairment. Since efavirenz is principally metabolized by the cytochrome P450 (CYP450) system, caution should be exercised in administering the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) to patients with mild-to-moderate liver disease. 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.

Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy 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 the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) needs to be weighed against the potential risks of significant liver toxicity. In such patients, interruption or discontinuation of treatment must be considered.

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. 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 combination antiretroviral therapy 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 the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) 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. Limited clinical experience suggests that emtricitabine and tenofovir disoproxil fumarate have an anti-HBV activity when used in antiretroviral combination therapy to control HIV infection. Discontinuation of the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) 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 the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) must be closely monitored with both clinical and laboratory follow-up for at least four months after stopping treatment with the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg). 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.

Psychiatric symptoms: Psychiatric adverse reactions have been reported in patients treated with efavirenz. Patients with a prior history of psychiatric disorders appear to be at greater risk of these serious psychiatric adverse reactions. In particular, severe depression was more common in those with a history of depression. There have also been post-marketing reports of severe depression, death by suicide, delusions and psychosis-like behaviour. Patients should be advised that if they experience symptoms such as severe depression, psychosis or suicidal ideation, they should contact their 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.

Nervous system symptoms: Symptoms including, but not limited to, dizziness, insomnia, somnolence, impaired concentration and abnormal dreaming are frequently reported undesirable effects in patients receiving efavirenz 600 mg daily in clinical studies. Dizziness was also seen in clinical studies with emtricitabine and tenofovir disoproxil fumarate. Headache has been reported in clinical studies with emtricitabine. 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 drug interaction study, carbamazepine plasma concentrations were decreased when carbamazepine was co-administered with Efavirenz. Caution must be taken in any patient with a history of seizures.

Renal impairment: The fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) is not recommended for patients with moderate or severe renal impairment. Patients with moderate or severe renal impairment require a dose adjustment of emtricitabine and tenofovir disoproxil fumarate that cannot be achieved with the combination tablet. Use of the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) should be avoided with concurrent or recent use of a nephrotoxic medicinal product. If concomitant use of the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) and nephrotoxic agents (e.g. aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir, interleukin-2) is unavoidable, renal function must be monitored weekly.

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

It is recommended that creatinine clearance is calculated in all patients prior to initiating therapy with the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) and renal function (creatinine clearance and serum phosphate) is also monitored every four weeks during the first year and then every three months. In patients with a history of renal dysfunction or in patients who are at risk for renal dysfunction, consideration must be given to more frequent monitoring of renal function.

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 the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg), renal function must be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations, combination product and the dosing interval of the individual components cannot be altered, treatment with the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) 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). Where discontinuation of therapy with one of the components of the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) is indicated or where dose modification is necessary, separate preparations of efavirenz, emtricitabine and tenofovir disoproxil fumarate are available.

Skin reactions: Mild-to-moderate rash has been reported with the individual components of the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg). 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. The incidence of erythema multiforme or Stevens-Johnson syndrome was approximately 0.1%. The fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) must be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. Patients who discontinued treatment with other non-nucleoside reverse transcriptase inhibitors due to rash may be at higher risk of developing rash during treatment with the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg). The fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) is not recommended for patients who have had a life-threatening cutaneous reaction (e.g., Stevens-Johnson syndrome) while taking an NNRTI.

Lipodystrophy and metabolic abnormalities: Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors (PI) and lipoatrophy and nucleoside reverse transcriptase inhibitors (NRTIs) has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug-related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

Effect of food: The administration of the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) with food may increase efavirenz exposure and may lead to an increase in frequency of adverse reactions. It is recommended that the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) be taken on an empty stomach, preferably at bedtime.

Mitochondrial dysfunction: Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV negative infants exposed in utero and/or postnatally to nucleoside analogues. The main adverse events reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactataemia, hyperlipasaemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether the neurological disorders are transient or permanent is currently unknown. Any child exposed *in utero* to nucleoside and nucleotide analogues, even HIV negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. 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 combination antiretroviral therapy (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 pneumonia caused by *Pneumocystis jiroveci* (formerly known as *Pneumocystis carinii*). Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

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 combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Bone: In a 144-week controlled clinical study that compared tenofovir disoproxil fumarate with stavudine in combination with lamivudine and efavirenz in antiretroviral-naïve patients, small decreases in bone mineral density of the hip and spine were observed in both treatment groups. Decreases in bone mineral density of spine and changes in bone biomarkers from baseline were significantly greater in the tenofovir disoproxil fumarate treatment group at 144 weeks. Decreases in bone mineral density of the hip were significantly greater in this group until 96 weeks. However, there was no increased risk of fractures or evidence for clinically relevant bone abnormalities over 144 weeks.

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

Other antiretroviral agents: No data are available on the safety and efficacy of the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) in combination with other antiretroviral agents.

Didanosine: Co-administration of the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) and didanosine is not recommended since exposure to didanosine is significantly increased following co-administration with tenofovir disoproxil fumarate that may increase the risk of didanosine-related adverse reactions. Rarely, pancreatitis and lactic acidosis, sometimes fatal have been reported.

Switching from a PI-based antiretroviral regimen: Currently available data indicate a trend that in patients on a PI-based antiretroviral regimen the switch to the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) may lead to a reduction of the response to the therapy. 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.

Patients with HIV-1 harbouring mutations: The fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) should be avoided in patients with HIV-1 harbouring the K65R, M184V/I or K103N mutation.

Excipients: This medicinal product contains 1 mmol (23.6 mg) of sodium per dose which should be taken into consideration by patients on a controlled sodium diet.

Interaction with other medicinal products and other forms of interaction

No drug interaction studies have been conducted using the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg). As the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) contains efavirenz, emtricitabine and tenofovir disoproxil fumarate, any interactions that have been identified with these agents individually may occur with the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg). Interaction studies with these agents have only been performed in adults.

The fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) should not be administered concomitantly with other medicinal products containing any of the components, efavirenz, emtricitabine or tenofovir disoproxil as fumarate. Due to similarities with emtricitabine, the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) should not be administered concomitantly with other cytidine analogues, such as lamivudine. The fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) should not be administered concomitantly with adefovir dipivoxil.

Efavirenz is an inducer of CYP3A4 and an inhibitor of some CYP450 isoenzymes including CYP3A4. Other compounds that are substrates of CYP3A4 may have decreased plasma concentrations when co-administered with efavirenz. Efavirenz exposure may also be altered when given with medicinal products or food (for example, grapefruit juice) which affect CYP3A4 activity. *In vitro* and clinical pharmacokinetic interaction studies have shown the potential for CYP450- mediated interactions involving emtricitabine and tenofovir disoproxil fumarate 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 in uninfected volunteers who received efavirenz. False positive test results have only been observed with the CEDIA DAU Multi-Level THC assay, which is used for screening, and have not been observed with other cannabinoid assays tested including tests used for confirmation of positive results.

Contraindications of concomitant use

The fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) 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.

Voriconazole: Co-administration of standard doses of efavirenz and voriconazole is contraindicated. Since the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg is a fixed-dose combination product, the dose of efavirenz cannot be altered; therefore, voriconazole and the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) must not be co-administered.

St. John's wort (Hypericum perforatum): Co-administration of the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) 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 drug 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.

Concomitant use not recommended

Atazanavir/ritonavir: Insufficient data are available to make a dosing recommendation for atazanavir/ritonavir in combination with the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg). Therefore co-administration of atazanavir/ritonavir and the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) is not recommended.

Didanosine: Co-administration of the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) and didanosine is not recommended.

Renally eliminated medicinal products: Since emtricitabine and tenofovir are primarily eliminated by the kidneys, co-administration of the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg), 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 the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) 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.

Other interactions

Interactions between the components of the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) and protease inhibitors, antiretroviral agents other than protease inhibitors and other non-antiretroviral medicinal products are listed in Table 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 the individual components of the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) and other medicinal products

Medicinal product by therapeutic areas (dose in mg)	Effects on drug levels Mean percent change in AUC, C_{max}, C_{min} with 90% confidence intervals if available(mechanism)	Recommendation concerning co-administration with the fixed-dose combination (Efavirenz 600 mg / Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg)
ANTI-INFECTIVES		
Antiretrovirals		
Protease inhibitors		
Fosamprenavir/ritonavir/Efavirenz (700 mg b.i.d./100 mg b.i.d./600 mg q.d.)	No clinically significant pharmacokinetic interaction.	The fixed-dose combination Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg and fosamprenavir/ ritonavir can be co-administered without dose adjustment. See ritonavir row below.
Fosamprenavir/ritonavir/Emtricitabine	Interaction not studied.	
Fosamprenavir/ritonavir/Tenofovir disoproxil fumarate	Interaction not studied.	
Atazanavir/Ritonavir /Tenofovir disoproxil fumarate (300 q.d./100 q.d./300 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 the fixed-dose combination Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg) 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.	
Indinavir/Efavirenz (800 q8h/200 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 the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg). 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 the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg), and indinavir.
Indinavir/Emtricitabine (800 q8h/200 q.d.)	Indinavir: AUC: ↔ C_{max}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔	
Indinavir/Tenofovir disoproxil fumarate (800 q8h/300 q.d.)	Indinavir: AUC: ↔ C_{max}: ↔ Tenofovir: AUC: ↔ C_{max}: ↔	
Darunavir/ritonavir/ Efavirenz (300 mg b.i.d.*/100 mg b.i.d./600 mg q.d.) *lower than recommended dose	Darunavir: AUC: ↓ 13% C_{min}: ↓ 31% (CYP3A4 induction) Efavirenz: AUC: ↑ 21% C_{min}: ↑ 17% (CYP3A4 inhibition)	The clinical significance of the changes in darunavir and efavirenz concentrations has not been established. Similar findings are expected with the approved darunavir/ritonavir 600/100 mg b.i.d. dose. Darunavir/ritonavir should be used with caution in combination with the fixed-(Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg). 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/ Tenofovir disoproxil fumarate (300 mg b.i.d.*/100 mg b.i.d./300 mg q.d.) *lower than recommended dose	AUC: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 22% C_{min}: ↑ 37%	
Darunavir/ritonavir/ Emtricitabine	Interaction not studied. Based on the different elimination pathways, no interaction is expected.	
Lopinavir/Ritonavir/ Tenofovir disoproxil fumarate (400 b.i.d./100 b.i.d./300 q.d.)	Lopinavir/Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 32% (↑ 25 to ↑ 38) C_{max}: ↔ C_{min}: ↑ 51% (↑ 37 to ↑ 66) Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders.	Insufficient data are available to make a dosing recommendation for lopinavir/ritonavir when dosed with the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg). Co-administration of lopinavir/ritonavir and the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg). 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.)	Co-administration of lopinavir/ritonavir with efavirenz resulted in a substantial decrease in lopinavir exposure, necessitating dosage adjustment of lopinavir/ ritonavir. When used in combination with efavirenz and two NRTIs, 533/133 mg lopinavir/ritonavir (soft capsules) twice daily yielded similar lopinavir plasma concentrations as compared to lopinavir/ritonavir (soft capsules) 400/100 mg twice daily without efavirenz (historical data). Lopinavir concentrations: ↓ 30-40% Lopinavir concentrations: similar to lopinavir/ritonavir 400/100 mg twice daily without efavirenz. Dosage 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 b.i.d./600 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 the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg). is not recommended. When using the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg). in a regimen including 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 fumarate	Interaction not studied.	
Saquinavir/Ritonavir /Efavirenz	No data are available on the potential interactions of efavirenz with the combination of saquinavir and ritonavir. 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 the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg). Co-administration of saquinavir/ritonavir and the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg) is not recommended.
Saquinavir/ritonavir /Tenofovir disoproxil fumarate	There were no clinically significant pharmacokinetic interactions when tenofovir disoproxil fumarate 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: AUC_{12h}: ↓ 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 fumarate (300 mg b.i.d./300 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)	The fixed-dose combination Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg and raltegravir can be co-administered without dose adjustment.
Raltegravir/Tenofovir disoproxil fumarate (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 fumarate. Clinically significant interactions 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 pathways.	Due to the similarity between lamivudine and emtricitabine, a component of the fixed-dose combination Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg, the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg) should not be administered concomitantly with lamivudine
NNRTIs/Efavirenz	Interaction not studied.	Since use of two NNRTIs proved not beneficial in terms of efficacy and safety, co-administration of the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg) and another NNRTI is not recommended.
Didanosine/Tenofovir disoproxil fumarate	Co-administration of tenofovir disoproxil fumarate and didanosine results in a 40-60% increase in systemic exposure to didanosine that may increase the risk for didanosine-related adverse events. Rare cases of pancreatitis and lactic acidosis, sometimes fatal, have been reported. Co-administration of tenofovir disoproxil fumarate 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 dosage of 250 mg didanosine co-administered with tenofovir disoproxil fumarate therapy has been associated with reports of high rates of virologic failure within several tested combinations.	Co-administration of the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg) and didanosine is not recommended.
Didanosine/Efavirenz	Interaction not studied.	
Didanosine/Emtricitabine	Interaction not studied.	
Antibiotics		
Clarithromycin/Efavirenz (500 b.i.d./400 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 the fixed-dose combination Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg).
Clarithromycin/Emtricitabine	Interaction not studied.	
Clarithromycin/Tenofovir disoproxil fumarate	Interaction not studied.	
Antimycobacterials		
Rifabutin/Efavirenz (300 q.d./600 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 the fixed-dose combination Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg). Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week in combination with the fixed-dose combination Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg).
Rifabutin/Emtricitabine	Interaction not studied.	
Rifabutin/Tenofovir disoproxil fumarate	Interaction not studied.	
Rifampicin/Efavirenz (600 q.d./600 q.d.)	Efavirenz: AUC: ↓ 26% (↓ 15 to ↓ 36) C_{max}: ↓ 20% (↓ 11 to ↓ 28) C_{min}: ↓ 32% (↓ 15 to ↓ 46) (CYP3A4 and CYP2B6 induction)	An additional 200 mg/day (800 mg total) of Efavirenz is recommended when rifampicin is co-administered with the fixed-dose combination Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg). No dose adjustment of rifampicin is recommended when given with the fixed-dose combination Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg).
Rifampicin/Tenofovir disoproxil fumarate (600 q.d./300 q.d.)	Rifampicin: AUC: ↔ C_{max}: ↔ Tenofovir: AUC: ↔ C_{max}: ↔	
Rifampicin/Emtricitabine	Interaction not studied.	
Antifungals		
Itraconazole/Efavirenz (200 b.i.d./600 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}: ↔	No dose recommendations can be made for the use of the fixed-dose combination Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg). in combination with itraconazole. An alternative antifungal treatment should be considered.
Itraconazole/Emtricitabine	Interaction not studied.	
Itraconazole/Tenofovir disoproxil fumarate	Interaction not studied.	
Posaconazole/Efavirenz (-/400 mg q.d.)	Posaconazole: AUC: ↓ 50% C_{max}: ↓ 45% (UDP-G induction)	Concomitant use of posaconazole and the fixed-dose combination Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg). Should be avoided unless the benefit to the patient outweighs the risk.
Posaconazole/Emtricitabine	Interaction not studied.	
Posaconazole/Tenofovir disoproxil fumarate	Interaction not studied.	
Voriconazole/Efavirenz (200 b.i.d./400 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.	Since the fixed-dose combination Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg) is a fixed-dose combination product, the dose of Efavirenz cannot be altered; therefore, voriconazole and the fixed-dose combination Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg) must not be co-administered.
Voriconazole/Emtricitabine	Interaction not studied.	
Voriconazole/Tenofovir disoproxil fumarate	Interaction not studied.	
ANTICONVULSANTS		
Carbamazepine/ Efavirenz (400 q.d./600 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 recommendations can be made for the use of the fixed-dose combination Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg). with carbamazepine. An alternative anticonvulsant should be considered. Carbamazepine plasma levels should be monitored periodically.
Carbamazepine/ Emtricitabine	Interaction not studied.	
Carbamazepine/ Tenofovir disoproxil fumarate	Interaction not studied.	
Phenytoin, Phenobarbital, and other anticonvulsants that are substrates of CYP450 isoenzymes	Interaction not studied with efavirenz, emtricitabine, or tenofovir disoproxil fumarate. There is a potential for reduction or increase in the plasma concentrations of phenytoin, Phenobarbital and other anticonvulsants that are substrates of CYP450 isoenzymes with efavirenz.	When the fixed-dose combination Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg). is co- administered with an anticonvulsant that is a substrate of CYP450 isoenzymes, 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.	The fixed-dose combination Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg). 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 fumarate	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.	The fixed-dose combination Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg). and vigabatrin or gabapentin can be coadministered without dose adjustment.
Vigabatrin/Emtricitabine Gabapentin/Emtricitabine	Interaction not studied.	
Vigabatrin/Tenofovir disoproxil fumarate Gabapentin/Tenofovir disoproxil fumarate	Interaction not studied.	
ANTICOAGULANTS		
Warfarin/Efavirenz	Interaction not studied. Plasma concentrations and effects of warfarin are potentially increased or decreased by efavirenz.	Dose adjustment of warfarin may be required when co-administered with the fixed-dose combination Efavirenz 600 mg /Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg).
ANTIDEPRESSANTS		
Selective Serotonin Reuptake Inhibitors (SSRIs)		
Sertraline/Efavirenz (50 q.d./600 q.d.)	Sertraline: AUC: ↓ 39% (↓ 27 to ↓ 50) C_{max}: ↓ 29% (↓ 15 to ↓ 40) C_{min}: ↓ 46% (↓ 31 to ↓ 58) Efavirenz: AUC: ↔ C_{max}: ↑ 11% (↑ 6 to ↑ 16) C_{min}: ↔ (CYP3A4 induction)	When co-administered with the fixed-dose combination (Efavirenz 600 mg /Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg), sertraline dose increases should be guided by clinical response.
Sertraline/Emtricitabine	Interaction not studied.	
Sertraline/Tenofovir disoproxil fumarate	Interaction not studied.	
Paroxetine/Efavirenz (20 q.d./600 q.d.)	Paroxetine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔	The fixed-dose combination Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg) and paroxetine can be co-administered without dose adjustment.
Paroxetine/Emtricitabine	Interaction not studied.	
Paroxetine/Tenofovir disoproxil fumarate	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.	The fixed-dose combination Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg) and fluoxetine can be co-administered without dose adjustment.
Fluoxetine/Emtricitabine	Interaction not studied.	
Fluoxetine/Tenofovir disoproxil fumarate	Interaction not studied.	
CARDIOVASCULAR AGENTS		
Calcium Channel Blockers		
Diltiazem/Efavirenz (240 q.d./600 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) 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.	Dose adjustments of diltiazem when co-administered with the fixed-dose combination Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg) should be guided by clinical response (refer to the Summary of Product Characteristics for diltiazem).
Diltiazem/Emtricitabine	Interaction not studied.	
Diltiazem/Tenofovir disoproxil fumarate	Interaction not studied.	

Verapamil, Felodipine, Nifedipine and Nicardipine	Interaction not studied with efavirenz, emtricitabine, or tenofovir disoproxil fumarate. 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 the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg) 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 q.d./600 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 when atorvastatin, pravastatin, or simvastatin is co-administered with the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg). Dosage adjustments of statins may be required (refer to the Summary of Product Characteristics for the statin).
Atorvastatin/Emtricitabine	Interaction not studied.	
Atorvastatin/Tenofovir disoproxil fumarate	Interaction not studied.	
Pravastatin/Efavirenz (40 q.d./600 q.d.)	Pravastatin: AUC: ↓ 40% (↓ 26 to ↓ 57) C_{max}: ↓ 18% (↓ 59 to ↑ 12)	
Pravastatin/Emtricitabine	Interaction not studied.	
Pravastatin/Tenofovir disoproxil fumarate	Interaction not studied.	
Simvastatin/Efavirenz (40 q.d./600 q.d.)	Simvastatin: AUC: ↓ 69% (↓ 62 to ↓ 73) C_{max}: ↓ 76% (↓ 63 to ↓ 79) Simvastatin acid: AUC: ↓ 58% (↓ 39 to ↓ 68) 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.	
Simvastatin/Emtricitabine	Interaction not studied.	
Simvastatin/Tenofovir disoproxil fumarate	Interaction not studied.	
Rosuvastatin/Efavirenz	Interaction not studied. Rosuvastatin is largely excreted unchanged via the faeces, therefore interaction with efavirenz is not expected.	The fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg) and rosuvastatin can be co-administered without dose adjustment.
Rosuvastatin/Emtricitabine	Interaction not studied.	
Rosuvastatin/Tenofovir disoproxil fumarate	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 oral contraceptives.
Ethinyloestradiol/Tenofovir disoproxil fumarate (-/300 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 drug interaction study, no significant differences in MPA pharmacokinetic parameters were found between subjects receiving efavirenz-containing antiretroviral therapy and subjects receiving no antiretroviral therapy. 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.	Because of the limited information available, a reliable method of barrier contraception must be used in addition to hormonal contraceptives
DMPA/Tenofovir disoproxil fumarate	Interaction not studied.	
DMPA/Emtricitabine	Interaction not studied.	
Implant: Etonogestrel/Efavirenz	Interaction not studied. 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.	Because of the limited information available, a reliable method of barrier contraception must be used in addition to hormonal contraceptives
Etonogestrel/Tenofovir disoproxil fumarate	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 the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg).
Tacrolimus/Emtricitabine/Tenofovir disoproxil fumarate (0.1 mg/kg q.d./200 mg/300 mg q.d.)	Tacrolimus: AUC: ↔ C_{max}: ↔ C_{24h}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{24h}: ↔ Tenofovir disoproxil fumarate: AUC: ↔ C_{max}: ↔ C_{24h}: ↔	
OPIOIDS		
Methadone/Efavirenz (35-100 q.d./600 q.d.)	Methadone: AUC: ↓ 52% (↓ 33 to ↓ 66) C_{max}: ↓ 45% (↓ 25 to ↓ 59) (CYP3A4 induction) In a study of HIV infected intravenous drug 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.	Patients receiving methadone and the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg) concomitantly should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.
Methadone/Tenofovir disoproxil fumarate (40-110 q.d./300 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 the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg).
Buprenorphine/naloxone/Emtricitabine	Interaction not studied.	
Buprenorphine/naloxone/Tenofovir disoproxil fumarate	Interaction not studied.	
HERBAL PRODUCTS		
St. John's wort (*Hypericum perforatum*)/Efavirenz	Plasma levels of efavirenz can be reduced by concomitant use of St. John's wort due to induction of drug metabolising enzymes and/or transport proteins by St. John's wort.	Co-administration of the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg). and St. John's wort is contraindicated. 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.
St. John's wort (*Hypericum perforatum*)/Emtricitabine	Interaction not studied.	
St. John's wort (*Hypericum perforatum*)/Tenofovir disoproxil fumarate	Interaction not studied.	

Studies conducted with other medicinal products: There were no clinically significant pharmacokinetic interactions when efavirenz was administered with azithromycin, cetirizine, lorazepam, nelfinavir, zidovudine, aluminium/magnesium hydroxide antacids, famotidine or fluconazole. The potential for interactions with efavirenz and other imidazole 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 fumarate was co-administered with adefovir dipivoxil, emtricitabine, nelfinavir or ribavirin.

Fertility, Pregnancy and lactation

The fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) should not be used during pregnancy unless clearly necessary (there are no other appropriate treatment options).

Women of childbearing potential / contraception in males and females: Pregnancy should be avoided in women receiving the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg). Women of childbearing potential should undergo pregnancy testing before initiation of the fixed-dose combination (Efavirenz 600 mg / Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg).

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) while on therapy with the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg). Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) is recommended.

Pregnancy:

Efavirenz: As of July 2010, the Antiretroviral Pregnancy Registry (APR) has received prospective reports of 718 pregnancies with first-trimester exposure to efavirenz-containing regimens, resulting in 604 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. In retrospective reports, there have been six cases of findings consistent with neural tube defects including meningomyelocele, all in mothers exposed to efavirenz-containing regimens in the first trimester. A causal relationship of these events to the use of efavirenz has not been established and the total number of pregnant women exposed to efavirenz-containing regimens 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..

Malformations have been observed in foetuses from efavirenz-treated monkeys.

Emtricitabine and tenofovir disoproxil fumarate: A moderate amount of data on pregnant women (between 300-1,000 pregnancy outcomes) indicate no malformations or foetal/neonatal toxicity associated with emtricitabine and tenofovir disoproxil fumarate. Animal studies on emtricitabine and tenofovir disoproxil fumarate do not indicate reproductive toxicity.

The fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) should not be used during pregnancy unless the clinical condition of the woman requires treatment with efavirenz/emtricitabine/tenofovir disoproxil fumarate.

Breast-feeding

Emtricitabine and tenofovir have been shown to be excreted in human milk. There is insufficient information on the effects of emtricitabine and tenofovir in newborns/infants. Studies in rats have demonstrated that efavirenz and tenofovir are excreted in milk; concentrations of efavirenz were much higher than those in maternal plasma. Therefore the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) should not be used during breast-feeding.

As a general rule, it is recommended that HIV infected women do not breast-feed their infants in order to avoid transmission of HIV to the infant.

Fertility

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

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 fumarate. 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.

Undesirable effects

a. Summary of the safety profile

The combination of efavirenz, emtricitabine and tenofovir disoproxil fumarate has been studied in 460 patients either as the fixed-dose combination tablet the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) (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 the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) 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 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 the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg).

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

The administration of the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) with food may increase efavirenz exposure and may lead to an increase in the frequency of adverse reactions.

b. Tabulated list of adverse reactions

The adverse reactions from clinical study and post-marketing experience with the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) and the individual components of the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) in antiretroviral combination therapy are listed in Table 2 below by body system organ class, frequency and the component(s) of the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) to which the adverse reactions are attributable. Within each frequency grouping, undesirable effects 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 the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg):

Treatment-emergent adverse reactions considered possibly or probably related to the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) reported in study AI266073 (over 48 weeks; n = 203), which have not been associated with one of the individual components of the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg), include:

Common: - anorexia

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

Table 2: Adverse reactions associated with the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) **listed by the component(s) of** the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg) **to which the adverse reactions are attributable**

	The fixed-dose combination (Efavirenz 600 mg/Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg)		
	Efavirenz	**Emtricitabine**	**Tenofovir disoproxil fumarate**
Blood and lymphatic system disorders:			
Common		Neutropenia	
Uncommon		Anaemia[1]	
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	Vertigo, tinnitus,		
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[3]
Hepatobiliary disorders:			
Common		elevated serum aspartate aminotransferase (AST) and/or elevated serum alanine aminotransferase (ALT), hyperbilirubinaemia	increased transaminases
Uncommon	hepatitis acute		
Rare	hepatic failure[3,4]		hepatic steatosis[3], 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
Metabolism and nutrition disorders:			
Very Common			hypophosphataemia[2]
Common		hyperglycaemia, hypertriglyceridaemia	
Uncommon			hypokalaemia[2]
Rare			lactic acidosis[3]
Vascular disorders:			
Uncommon	Flushing		
General disorders and administration site conditions:			
Very common			Asthenia
Common	Fatigue	Asthenia, pain	
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]		
Rare	completed suicide[3,4], delusion[3,4], neurosis[3,4]		
Immune system disorders:			
Common		allergic reaction	
Uncommon	hypersensitivity		
Metabolism and nutrition disorders:			
Very common			hypophosphataemia[2]
Common		hyperglycaemia, hypertriglyceridaemia	
Uncommon			hypokalaemia[2]
Rare			lactic acidosis[3]
Musculoskeletal and connective tissue disorders:			
Very common		elevated creatine kinase	
Common			rhabdomyolysis[2], muscular weakness[2]
Rare			(manifested as bone pain and infrequently contributing to fractures)[2,4], myopathy[2]
Renal and urinary disorders:			
Uncommon			increased creatinine, proteinuria
Rare			renal failure (acute and chronic), acute tubular necrosis, proximal renal tubulopathy including Fanconi syndrome, nephritis (including acute interstitial nephritis)[4], nephrogenic diabetes insipidus
Reproductive system and breast disorders:			
Uncommon	gynaecomastia		

[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 fumarate in the absence of this condition.

[3] See section c. 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 fumarate. The frequency category was estimated from a statistical calculation based on the total number ofpatients treated with efavirenz in clinical trials (n = 3,969) or exposed to emtricitabine in randomised controlled clinical trials (n = 1,563) or exposed to tenofovir disoproxil fumarate in randomised controlled clinical trials and the expanded access programme (n = 7,319).

c. *Description of selected adverse reactions*

Rash: In clinical trials of efavirenz, rashes were usually mild-to-moderate maculopapular skin eruptions that occurred within the first two weeks of initiating therapy with efavirenz. In most patients rash resolved with continuing therapy with efavirenz within one month. The fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) can be reinitiated in patients interrupting therapy because of rash. Use of appropriate antihistamines and/or corticosteroids is recommended when the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) 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 the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg). 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 the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) is taken concomitantly with meals possibly due to increased efavirenz plasma levels. Dosing at bedtime seems to improve the tolerability of these symptoms.

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 the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) may cause renal damage, monitoring of renal function is recommended.

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

Lactic acidosis and severe hepatomegaly with steatosis: Lactic acidosis, usually associated with hepatic steatosis, has been reported with the use of nucleoside analogues. Treatment with nucleoside analogues should be discontinued in the setting of symptomatic hyperlactataemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.

Lipids, lipodystrophy and metabolic abnormalities: Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia.

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).

Immune Reactivation Syndrome: In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise.

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

d. Paediatric population

Insufficient safety data are available for children below 18 years of age. The fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) is not recommended in this population.

e. Other special populations

Elderly: The fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) 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 the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg).

Patients with renal impairment: Since tenofovir disoproxil fumarate can cause renal toxicity, close monitoring of renal function is recommended in any patient with mild renal impairment treated with the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg).

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 fumarate 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.

Overdose

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

If overdose occurs, the patient must be monitored for evidence of toxicity, 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: 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 fumarate 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*.

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. No other pathways of resistance to emtricitabine or tenofovir have been identified. 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 fumarate should be avoided in patients with HIV-1 harbouring the K65R mutation. Both the K65R and M184V/I mutation remain fully susceptible to efavirenz.

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 fumarate.

In vivo resistance (antiretroviral-naïve patients): Extremely limited resistance data from patients treated with the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) are currently available. However, in a 144-week open-label randomised clinical study (GS-01-934) in antiretroviral-naïve patients, where efavirenz, emtricitabine and tenofovir disoproxil fumarate were used as individual formulations (or as efavirenz and the fixed combination of emtricitabine and tenofovir disoproxil fumarate 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 drug 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 fumarate 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 fumarate group to the lamivudine/zidovudine group among all subjects).
- No virus analysed contained the K65R mutation.
- Genotypic resistance to efavirenz, predominantly the K103N mutation, developed in virus from 13/19 (68%) patients in the efavirenz + emtricitabine + tenofovir disoproxil fumarate 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

	Tenofovir disoproxil fumarate 300 mg/ Emtricitabine 200 mg/Efavirenz 600 mg (N=244)		**Efavirenz+Combivir (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	
TAMs[2]	0		2	(7%)

* p-value < 0.05, Fisher's Exact test comparing emtricitabine+tenofovir disoproxil fumarate arm to Combivir arm 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).

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 fumarate or a fixed combination of lamivudine and zidovudine (Combivir) administered twice daily and efavirenz once daily (please refer to the Summary of Product Characteristics for Truvada). 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 the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) on an empty stomach. Preliminary 24-week data are available from a total of 286 patients who changed to the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg): 160 had previously received efavirenz, emtricitabine and tenofovir disoproxil fumarate, and 126 had previously received Combivir and efavirenz. The majority of patients from both initial treatment groups maintained virologic suppression after changing to the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg). In 91% of the patients the HIV-1 RNA plasma concentrations remained < 50 copies/ml and in 97% < 400 copies/ml, after 24 weeks of the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) treatment (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 the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) to antiretroviral therapy consisting of two nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) with a protease inhibitor or non-nucleoside reverse transcriptase inhibitor; however not a regimen containing all the components of the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg). The fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) was administered on an empty stomach. 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 the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg), and had been virologically suppressed for at least three months at baseline. Patients either changed to the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) (N=203) or continued on their original antiretroviral treatment regimen (N=97). Twenty-four 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 the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) (see Table 4).

Table 4: 48-week efficacy data from study AI266073 in which the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) was administered to virologically suppressed patients on combination antiretroviral therapy

Endpoint	**Treatment group**		**Difference between fixed-**
	Fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg) (N=203) n/N (%)	**Stayed on original treatment regimen (N=97) n/N (%)**	**dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/ Tenofovir disoproxil fumarate 300 mg) 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 the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) [92.4% versus 94.0% for the PVR (sensitivity analysis) for to the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) 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 the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) 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 the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) **according to the type of prior antiretroviral regimen (Kaiser Permanente patient database)**

	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 the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) in treatment-naïve patients or in heavily pretreated patients. There is no clinical experience with the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) 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 fumarate 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).

Paediatric population: The safety and efficacy of the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) in children under the age of 18 years have not been established.

Pharmacokinetic properties

The separate pharmaceutical forms of efavirenz, emtricitabine and tenofovir disoproxil fumarate were used to determine the pharmacokinetics of efavirenz, emtricitabine and tenofovir disoproxil fumarate, administered separately in HIV infected patients. The bioequivalence of one fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) 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 (equivalent to 300 mg tenofovir disoproxil fumarate) 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 fumarate (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-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 300 mg tenofovir disoproxil fumarate 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 300 mg dose of tenofovir disoproxil fumarate to HIV-1 infected patients in the fasted state, maximum tenofovir concentrations were achieved within one hour and the C_{max} 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 fumarate in fasted patients was approximately 25%.

Effect of food: The fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) 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 fumarate and emtricitabine in combination with either a high fat meal or a light meal increased the mean AUC and C_{max} of tenofovir by 35% and 15%, respectively without affecting emtricitabine exposures.

The fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) 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.It is anticipated that tenofovir exposure will be approximately 35% lower following administration of the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) on an empty stomach as compared to the individual component tenofovir disoproxil fumarate when taken with food. Forty-eight week data from a study (AI266073) showed maintenance of virologic suppression for patients who had stable virologic suppression on combination antiretroviral therapy and subsequently changed to the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) with a recommendation for administration of the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) on an empty stomach.

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 cytochrome P450 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 isoenzymes responsible for efavirenz metabolism and that it inhibits P450 isoenzymes 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 isoenzyme. 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 P450 enzymes, resulting in the induction of its own metabolism. 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).

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 fumarate nor tenofovir are substrates for the CYP450 enzymes. Neither emtricitabine nor tenofovir inhibited *in vitro* drug metabolism mediated by any of the major human CYP450 isoforms involved in drug 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 kidney 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.

Age Pharmacokinetic studies have not been performed with efavirenz, emtricitabine or tenofovir in the elderly (over 65 years).

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 the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) in infants and children under 18 years of age.

Renal impairment: The pharmacokinetics of efavirenz, emtricitabine and tenofovir disoproxil fumarate after co-administration of the separate pharmaceutical forms or as the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) have not been studied in HIV infected patients with renal impairment.

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

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

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

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

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

The fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) 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 fumarate that cannot be achieved with the combination tablet.

Hepatic impairment: The pharmacokinetics of the fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) have not been studied in HIV infected patients with hepatic impairment. The fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) should be administered with caution to patients with mild hepatic impairment.

The fixed-dose combination (Efavirenz 600 mg/ Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg) must not be used in patients with severe hepatic impairment and is not recommended for patients with moderate hepatic impairment. In the single patient studied with severe hepatic impairment (CPT, Class C), half-life of efavirenz was doubled indicating a potential for a much greater degree of accumulation. A multiple-dose study of efavirenz showed no significant effect on efavirenz pharmacokinetics in patients with mild hepatic impairment (Child-Pugh-Turcotte Class A) compared with controls. There were insufficient data to determine whether moderate or severe hepatic impairment (Child-Pugh-Turcotte Class B or C) affects efavirenz pharmacokinetics.

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

A single 300 mg dose of tenofovir disoproxil fumarate 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 fumarate is required in these subjects.

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 fumarate: Non-clinical safety pharmacology studies on tenofovir disoproxil fumarate reveal no special hazard for humans. Findings in repeated-dose toxicity studies in rats, dogs and monkeys at exposure levels greater than or equal to clinical exposure levels and with possible relevance to clinical use include renal and bone toxicity and a decrease in serum phosphate concentration. Bone toxicity was diagnosed as osteomalacia (monkeys) and reduced bone mineral density (BMD) (rats and dogs). The bone toxicity in young adult rats and dogs occurred at exposures ≥ 5-fold the exposure in paediatric or adult patients; bone toxicity occurred in juvenile infected monkeys at very high exposures following subcutaneous dosing (≥ 40-fold the exposure in patients). Findings in the rat and monkey studies indicated that there was a substance-related decrease in intestinal absorption of phosphate with potential secondary reduction in BMD.

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

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

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

Combination of emtricitabine and tenofovir disoproxil fumarate: 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.

Special precautions for storage

Store protected from moisture, at a temperature not exceeding 30°C.
Keep the container tightly closed.

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