Summary of Product Characteristics

VONAVIR

Efavirenz, Emtricitabine & Tenofovir Disoproxil Fumarate Tablets

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1. Name of the medicinal product

VONAVIR
(Efavirenz-600 mg, Emtricitabine-200mg & Tenofovir Disoproxil Fumarate 300mg Tablets)

2. Qualitative and quantitative composition

Each film coated tablet contains:
Efavirenz USP.....600 mg
Emtricitabine .....200 mg
Tenofovir Disoproxil Fumarate. 300mg
Equivalent to Tenofovir Disoproxil...245mg

3. Pharmaceutical form

Film-coated tablet.

The tablets are white to off white, modified capsule-shaped, film-coated, debossed with "145" on one side and “EM” on the other side.

4. Clinical particulars

4.1 Therapeutic indications

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

The demonstration of the benefit of Vonavir 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 Vonavir (see section 5.1). No data are currently available from clinical studies with Vonavir in treatment-naïve or in heavily pretreated patients.

No data are available to support the combination of Vonavir and other antiretroviral agents.

4.2 Posology and method of administration

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

Posology

Adults

The recommended dose of Vonavir is one tablet taken orally once daily.

If a patient misses a dose of Vonavir within 12 hours of the time it is usually taken, the patient should take Vonavir as soon as possible and resume the normal dosing schedule. If a patient misses a dose of Vonavir by more than 12 hours and it is almost time for the next dose, the patient should not take the missed dose and simply resume the usual dosing schedule.

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

It is recommended that Vonavir be taken on an empty stomach since food may increase efavirenz exposure and may lead to an increase in the frequency of adverse reactions (see sections 4.4 and 4.8). In order to improve the tolerability to efavirenz with respect to undesirable effects on the nervous system, bedtime dosing is recommended (see section 4.8).

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

Where discontinuation of therapy with one of the components of Vonavir 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 Vonavir is discontinued, consideration should be given to the long half-life of efavirenz (see section 5.2) and long intracellular half-lives of emtricitabine and tenofovir. Because of interpatient variability in these parameters and concerns regarding development of resistance, HIV treatment guidelines should be consulted, also taking into consideration the reason for discontinuation.

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

Special populations

Older people

Vonavir should be administered with caution to older people (see section 4.4).

Renal impairment

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

Hepatic impairment

The pharmacokinetics of Vonavir have not been studied in patients with hepatic impairment. Patients with mild liver disease (Child-Pugh-Turcotte (CPT), Class A) may be treated with the normal recommended dose of Vonavir (see sections 4.3, 4.4 and 5.2). Patients should be monitored carefully for adverse reactions, especially nervous system symptoms related to efavirenz (see sections 4.3 and 4.4).

If Vonavir is discontinued in patients co-infected with HIV and HBV, these patients should be closely monitored for evidence of exacerbation of hepatitis (see section 4.4).

Paediatric population

The safety and efficacy of Vonavir in children under the age of 18 years have not been established (see section 5.2).

Method of administration

Vonavir tablets should be swallowed whole with water, once daily.

4.3 Contraindications

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

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

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

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

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

4.4 Special warnings and precautions for use

Co-administration with other medicinal products

As a fixed combination, Vonavir should not be administered concomitantly with other medicinal products containing the same active components, emtricitabine or tenofovir disoproxil fumarate. Vonavir should not be co-administered with products containing efavirenz unless needed for dose adjustment e.g. with rifampicin (see section 4.2). Due to similarities with emtricitabine, Vonavir should not be administered concomitantly with other cytidine analogues, such as lamivudine (see section 4.5). Vonavir should not be administered concomitantly with adefovir dipivoxil.

Co-administration of Vonavir 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 (see section 4.5). Rarely, pancreatitis and lactic acidosis, sometimes fatal have been reported.

No data are available on the safety and efficacy of Vonavir in combination with other antiretroviral agents.

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

Switching from a PI-based antiretroviral regimen

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

Opportunistic infections

Patients receiving Vonavir 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 Vonavir, 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.

Effect of food

The administration of Vonavir with food may increase efavirenz exposure (see section 5.2) and may lead to an increase in frequency of adverse reactions (see section 4.8). It is recommended that Vonavir be taken on an empty stomach, preferably at bedtime.

Liver disease

The pharmacokinetics, safety and efficacy of Vonavir have not been established in patients with significant underlying liver disorders (see section 5.2). Vonavir is contraindicated in patients with severe hepatic impairment (see section 4.3) and not recommended in patients with moderate hepatic impairment. Since efavirenz is principally metabolised by the cytochrome P450 (CYP450) system, caution should be exercised in administering Vonavir to patients with mild hepatic impairment. These patients should be carefully monitored for efavirenz adverse reactions, especially nervous system symptoms. Laboratory tests should be performed to evaluate their liver disease at periodic intervals (see section 4.2).

Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy (CART) and should be monitored according to standard practice. If there is evidence of worsening liver disease or persistent elevations of serum transaminases to greater than 5 times the upper limit of the normal range, the benefit of continued therapy with Vonavir needs to be weighed against the potential risks of significant liver toxicity. In such patients, interruption or discontinuation of treatment must be considered (see section 4.8).

In patients treated with other medicinal products associated with liver toxicity, monitoring of liver enzymes is also recommended.

Hepatic events

Post-marketing reports of hepatic failure also occurred in patients with no pre-existing hepatic disease or other identifiable risk factors (see section 4.8). Liver enzyme monitoring should be considered for all patients independent of pre-existing hepatic dysfunction or other risk factors.

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

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

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

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

The safety and efficacy of Vonavir have not been studied for the treatment of chronic HBV infection. Emtricitabine and tenofovir individually and in combination have shown activity against HBV in pharmacodynamic studies (see section 5.1). Limited clinical experience suggests that emtricitabine and tenofovir disoproxil fumarate have an anti-HBV activity when used in antiretroviral combination therapy to control HIV infection. Discontinuation of Vonavir 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 Vonavir must be closely monitored with both clinical and laboratory follow-up for at least four months after stopping treatment with Vonavir. 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 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 (see section 4.8).

Nervous system symptoms

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

Seizures

Convulsions have been observed in patients receiving efavirenz, generally in the presence of a known medical history of seizures. Patients who are receiving concomitant anticonvulsant medicinal products primarily metabolised by the liver, such as phenytoin, carbamazepine and phenobarbital, may require periodic monitoring of plasma levels. In a drug interaction study, carbamazepine plasma concentrations were decreased when carbamazepine was co-administered with efavirenz (see section 4.5). Caution must be taken in any patient with a history of seizures.

Renal impairment

Vonavir is not recommended for patients with moderate or severe renal impairment (creatinine clearance < 50 ml/min). Patients with moderate or severe renal impairment require a dose adjustment of emtricitabine and tenofovir disoproxil fumarate that cannot be achieved with the combination tablet (see sections 4.2 and 5.2). Use of Vonavir should be avoided with concurrent or recent use of a nephrotoxic medicinal product. If concomitant use of Vonavir and nephrotoxic agents (e.g. aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir, interleukin-2) is unavoidable, renal function must be monitored weekly (see section 4.5).

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 (see section 4.8).

It is recommended that creatinine clearance is calculated in all patients prior to initiating therapy with Vonavir 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 of renal dysfunction, including patients who have previously experienced renal events while receiving adefovir dipivoxil, consideration should 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 Vonavir, renal function must be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations (see section 4.8, proximal tubulopathy). Since Vonavir is a combination product and the dosing interval of the individual components cannot be altered, treatment with Vonavir 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 Vonavir is indicated or where dose modification is necessary, separate preparations of efavirenz, emtricitabine and tenofovir disoproxil fumarate are available.

Bone effects

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 (see section 4.8). If bone abnormalities are suspected then appropriate consultation should be obtained.

Skin reactions

Mild-to-moderate rash has been reported with the individual components of Vonavir. The rash associated with the efavirenz component usually resolves with continued therapy. Appropriate antihistamines and/or corticosteroids may improve tolerability and hasten the resolution of rash. Severe rash associated with blistering, moist desquamation or ulceration has been reported in less than 1% of patients treated with efavirenz (see section 4.8). The incidence of erythema multiforme or Stevens-Johnson syndrome was approximately 0.1%. Vonavir must be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. Experience with efavirenz in patients who discontinued other antiretroviral agents of the NNRTI class is limited. Vonavir is not recommended for patients who have had a life-threatening cutaneous reaction (e.g., Stevens-Johnson syndrome) while taking an NNRTI.

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 should 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). Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk.Patients at increased risk should be followed closely.

Lipodystrophy

CART 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 and lipoatrophy and nucleoside reverse transcriptase inhibitors 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 (see section 4.8).

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

Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Osteonecrosis

Although the etiology is considered to be multifactorial (including corticosteroid use, alcohol

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

Patients with HIV-1 harbouring mutations

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

Older people

Vonavir has not been studied in patients over the age of 65. Older people are more likely to have decreased hepatic or renal function, therefore caution should be exercised when treating older people with Vonavir (see section 4.2).

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.

4.5 Interaction with other medicinal products and other forms of interaction

No drug interaction studies have been performed using Vonavir. As Vonavir contains efavirenz, emtricitabine and tenofovir disoproxil fumarate, any interactions that have been identified with these agents individually may occur with Vonavir. Interaction studies with these agents have only been performed in adults.

As a fixed combination, Vonavir should not be administered concomitantly with other medicinal products containing the components, emtricitabine or tenofovir disoproxil as fumarate. Vonavir should not be co-administered with products containing efavirenz unless needed for dose adjustment e.g. with rifampicin (see section 4.2). Due to similarities with emtricitabine, Vonavir should not be administered concomitantly with other cytidine analogues, such as lamivudine. Vonavir should not be administered concomitantly with adefovir dipivoxil.

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

Efavirenz exposure may be increased when given with medicinal products (for example ritonavir) or food (for example, grapefruit juice) which inhibit CYP3A4 or CYP2B6 activity. Compounds or herbal preparations (for example Ginkgo biloba extracts and St.

John's wort) which induce these enzymes may give rise to decreased plasma concentrations of efavirenz. Concomitant use of St. John's wort is contraindicated (see section 4.3). Concomitant use of Ginkgo biloba extracts is not recommended (see section 4.4).

In vitro and clinical pharmacokinetic interaction studies have shown the potential for 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

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

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

St. John's wort (Hypericum perforatum): Co-administration of Vonavir 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 (see section 4.3).

Concomitant use not recommended

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

Didanosine: Co-administration of Vonavir and didanosine is not recommended (see section 4.4 and Table 1).

Renally eliminated medicinal products: Since emtricitabine and tenofovir are primarily

eliminated by the kidneys, co-administration of Vonavir 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 Vonavir should be avoided with concurrent or recent use of a nephrotoxic medicinal product. Some examples include, but are not limited to, aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2 (see section 4.4).

Other interactions

Interactions between the components of Vonavir and protease inhibitors, antiretroviral agents other than protease inhibitors and other non-antiretroviral medicinal products are listed in Table 1 below (increase is indicated as "↑", decrease as "↓", no change as "↔", twice daily as "b.i.d.", once daily as "q.d." and once every 8 hours as "q8h"). If available, 90% confidence intervals are shown in parentheses.

Table 1: Interactions between the individual components of Vonavir and other medicinal products

Medicinal product by therapeutic areas	**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 Vonavir** **(efavirenz 600 mg, emtricitabine 200 mg, tenofovir disoproxil fumarate 300 mg)**
ANTI-INFECTIVES		
HIV antivirals		
Protease inhibitors		
Atazanavir/ritonavir/Tenofovir disoproxil fumarate (300 mg q.d./100 mg q.d./300 mg q.d.)	Atazanavir: AUC: ↓ 25% (↓ 42 to ↓ 3) C_{max}: ↓ 28% (↓ 50 to ↑ 5) C_{min}: ↓ 26% (↓ 46 to	Co-administration of atazanavir/ritonavir and Vonavir is not recommended.

	↑ 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.	
Atazanavir/ritonavir/Efavirenz (400 mg q.d./100 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/ritonavir/Efavirenz (400 mg q.d./200 mg q.d./600 mg q.d., all administered with food)	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 C_{min} might	

	negatively impact the efficacy of atazanavir. ** based on historical comparison. Co-administration of efavirenz with atazanavir/ritonavir is not recommended.	
Atazanavir/ritonavir/Emtricitabine	Interaction not studied.	
Darunavir/ritonavir/Efavirenz (300 mg b.i.d.*/100 mg b.i.d./600 mg q.d.) *lower than recommended doses; similar findings are expected with recommended doses.	Darunavir: AUC: ↓ 13% C_{min}: ↓ 31% C_{max}: ↓ 15% (CYP3A4 induction) Efavirenz: AUC: ↑ 21% C_{min}: ↑ 17% C_{max}: ↑ 15% (CYP3A4 inhibition)	Vonavir in combination with darunavir/ritonavir 800/100 mg once daily may result in suboptimal darunavir C_{min}. If Vonavir is to be used in combination with darunavir/ritonavir, the darunavir/ritonavir 600/100 mg twice daily regimen should be used. Darunavir/ritonavir should be used with caution in combination with Vonavir. 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	Darunavir: 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.	
Fosamprenavir/ritonavir/Efavirenz (700 mg b.i.d./100 mg b.i.d./600 mg q.d.)	No clinically significant pharmacokinetic interaction.	Vonavir 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.	
Indinavir/Efavirenz (800 mg q8h/200 mg q.d.)	Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Indinavir: AUC: ↓ 31% (↓ 8 to ↓ 47) C_{min}: ↓ 40% A similar reduction in indinavir exposures was observed when indinavir 1,000 mg q8h was given with efavirenz 600 mg q.d. (CYP3A4 induction)	Insufficient data are available to make a dosing recommendation for indinavir when dosed with Vonavir. 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 Vonavir, and indinavir.

	For co-administration of efavirenz with low-dose ritonavir in combination with a protease inhibitor, see section on ritonavir below.	
Indinavir/Emtricitabine (800 mg q8h/200 mg q.d.)	Indinavir: AUC: ↔ C_{max}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔	
Indinavir/Tenofovir disoproxil fumarate (800 mg q8h/300 mg q.d.)	Indinavir: AUC: ↔ C_{max}: ↔ Tenofovir: AUC: ↔ C_{max}: ↔	
Lopinavir/ritonavir/Tenofovir disoproxil fumarate (400 mg b.i.d./100 mg b.i.d./300 mg q.d.)	Lopinavir/Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 32% (↑ 25 to ↑ 38)	Insufficient data are available to make a dosing recommendation for lopinavir/ritonavir when dosed with Vonavir. Co-administration of lopinavir/ritonavir and Vonavir is not recommended.

	C_{max}: ↔ C_{min}: ↑ 51% (↑ 37 to ↑ 66) Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders.	
Lopinavir/ritonavir soft capsules or oral solution/Efavirenz	Substantial decrease in lopinavir exposure, necessitating dosage adjustment of lopinavir/ritonavir. When used in combination with efavirenz and two NRTIs, 533/133 mg lopinavir/ritonavir (soft capsules) twice daily yielded similar lopinavir plasma concentrations as compared to lopinavir/ritonavir (soft capsules) 400/100 mg twice daily without efavirenz (historical data).	
Lopinavir/ritonavir tablets/Efavirenz (400/100 mg b.i.d./600 mg q.d.) (500/125 mg b.i.d./600 mg q.d.)	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 mg b.i.d./600 mg q.d.)	Ritonavir: Morning AUC: ↑ 18% (↑ 6 to ↑ 33) Evening AUC: ↔ Morning C_{max}: ↑ 24% (↑ 12 to ↑ 38) Evening C_{max}: ↔ Morning C_{min}: ↑ 42% (↑ 9 to ↑ 86) Evening C_{min}: ↑ 24% (↑ 3 to ↑ 50) Efavirenz: AUC: ↑ 21% (↑ 10 to ↑ 34) C_{max}: ↑ 14% (↑ 4 to ↑ 26) C_{min}: ↑ 25% (↑ 7 to ↑ 46) (inhibition of CYP-	Co-administration of ritonavir at doses of 600 mg and Vonavir is not recommended. When using Vonavir with low-dose ritonavir, the possibility of an increase in the incidence of efavirenz-associated adverse events should be considered, due to possible pharmacodynamic interaction.

	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.	
Ritonavir/Emtricitabine	Interaction not studied.	
Ritonavir/Tenofovir disoproxil fumarate	Interaction not studied.	
Saquinavir/ritonavir/Efavirenz	Interaction not studied. For co-administration of efavirenz with low-dose ritonavir in combination with a protease inhibitor, see section on ritonavir above.	Insufficient data are available to make a dosing recommendation for saquinavir/ritonavir when dosed with Vonavir. Co-administration of saquinavir/ritonavir and Vonavir is not recommended. Use of Vonavir in combination with saquinavir as the sole protease inhibitor 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)	Vonavir and raltegravir can be co-administered without dose adjustment.
Raltegravir/Tenofovir disoproxil fumarate	Raltegravir:	

(400 mg b.i.d./-)	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 have not been found and would not be expected since the NRTIs are metabolised via a different route than efavirenz and would be unlikely to compete for the same metabolic enzymes and elimination pathways.	Due to the similarity between lamivudine and emtricitabine, a component of Vonavir, Vonavir should not be administered concomitantly with lamivudine (see section 4.4).

NNRTIs/Efavirenz	Interaction not studied.	Since use of two NNRTIs proved not beneficial in terms of efficacy and safety, co-administration of Vonavir 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 reactions. Rarely, 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	Co-administration of Vonavir and didanosine is not recommended (see section 4.4).

	combinations.	
Didanosine/Efavirenz	Interaction not studied.	
Didanosine/Emtricitabine	Interaction not studied.	
Hepatitis C antivirals		
Boceprevir/Efavirenz (800 mg 3 times daily/600 mg q.d.)	Boceprevir: AUC: ↔ 19%* C_{max}: ↔ 8% C_{min}: ↓ 44% Efavirenz: AUC: ↔ 20% C_{max}: ↔ 11% (CYP3A induction - effect on boceprevir) *0-8 hours No effect (↔) equals a decrease in mean ratio estimate of ≤ 20% or increase in mean ratio estimate of ≤ 25%	Plasma trough concentrations of boceprevir were decreased when administered with efavirenz, a component of Vonavir. The clinical outcome of this observed reduction of boceprevir trough concentrations has not been directly assessed.
Telaprevir/Efavirenz (1,125 mg q8h/600 mg q.d.)	Telaprevir (relative to 750 mg q8h): AUC: ↓ 18% (↓ 8 to ↓ 27) C_{max}: ↓ 14% (↓ 3 to ↓ 24) C_{min}: ↓ 25% (↓ 14 to	If Vonavir and telaprevir are co-administered, telaprevir 1,125 mg every 8 hours should be used.

	↓ 34) Efavirenz: AUC: ↓ 18% (↓ 10 to ↓ 26) C_{max}: ↓ 24% (↓ 15 to ↓ 32) C_{min}: ↓ 10% (↑ 1 to ↓ 19) (CYP3A induction by efavirenz)	
Antibiotics		
Clarithromycin/Efavirenz (500 mg b.i.d./400 mg q.d.)	Clarithromycin: AUC: ↓ 39% (↓ 30 to ↓ 46) C_{max}: ↓ 26% (↓ 15 to ↓ 35) Clarithromycin 14-hydroxymetabolite: AUC: ↑ 34% (↑ 18 to ↑ 53) C_{max}: ↑ 49% (↑ 32 to ↑ 69) Efavirenz: AUC: ↔ C_{max}: ↑ 11% (↑ 3 to ↑ 19) (CYP3A4 induction) Rash developed in 46% of uninfected	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 Vonavir.

	volunteers receiving efavirenz and clarithromycin.	
Clarithromycin/Emtricitabine	Interaction not studied.	
Clarithromycin/Tenofovir disoproxil fumarate	Interaction not studied.	
Antimycobacterials		
Rifabutin/Efavirenz (300 mg q.d./600 mg q.d.)	Rifabutin: AUC: ↓ 38% (↓ 28 to ↓ 47) C_{max}: ↓ 32% (↓ 15 to ↓ 46) C_{min}: ↓ 45% (↓ 31 to ↓ 56) Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↓ 12% (↓ 24 to ↑ 1) (CYP3A4 induction)	The daily dose of rifabutin should be increased by 50% when given with Vonavir. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week in combination with Vonavir. The clinical effect of this dose adjustment has not been adequately evaluated. Individual tolerability and virological response should be considered when making the dose adjustment (see section 5.2).
Rifabutin/Emtricitabine	Interaction not studied.	
Rifabutin/Tenofovir disoproxil fumarate	Interaction not studied.	
Rifampicin/Efavirenz (600 mg q.d./600 mg q.d.)	Efavirenz: AUC: ↓ 26% (↓ 15 to ↓ 36) C_{max}: ↓ 20% (↓ 11 to	When Vonavir is taken with rifampicin in patients weighing 50 kg or greater, an additional 200 mg/day (800 mg total) of

	↓ 28) C_{min}: ↓ 32% (↓ 15 to ↓ 46) (CYP3A4 and CYP2B6 induction)	efavirenz may provide exposure similar to a daily efavirenz dose of 600 mg when taken without rifampicin. The clinical effect of this dose adjustment has not been adequately evaluated. Individual tolerability and virological response should be considered when making the dose adjustment (see section 5.2). No dose adjustment of rifampicin is recommended when given with Vonavir.
Rifampicin/Tenofovir disoproxil fumarate (600 mg q.d./300 mg q.d.)	Rifampicin: AUC: ↔ C_{max}: ↔ Tenofovir: AUC: ↔ C_{max}: ↔	
Rifampicin/Emtricitabine	Interaction not studied.	
Antifungals		
Itraconazole/Efavirenz (200 mg b.i.d./600 mg q.d.)	Itraconazole: AUC: ↓ 39% (↓ 21 to ↓ 53) C_{max}: ↓ 37% (↓ 20 to ↓ 51) C_{min}: ↓ 44% (↓ 27 to ↓ 58) (decrease in itraconazole concentrations: CYP3A4 induction) Hydroxyitraconazole: AUC: ↓ 37% (↓ 14 to ↓ 55)	Since no dose recommendation can be made for itraconazole when used with Vonavir, an alternative antifungal treatment should be considered.

	C_{max}: ↓ 35% (↓ 12 to ↓ 52) C_{min}: ↓ 43% (↓ 18 to ↓ 60) Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔	
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 Vonavir 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 mg b.i.d./400 mg q.d.)	Voriconazole: AUC: ↓ 77% C_{max}: ↓ 61% Efavirenz: AUC: ↑ 44% C_{max}: ↑ 38%	Since Vonavir is a fixed-dose combination product, the dose of efavirenz cannot be altered; therefore, voriconazole and Vonavir must not be co-administered.

	(competitive inhibition of oxidative metabolism) Co-administration of standard doses of efavirenz and voriconazole is contraindicated (see section 4.3).	
Voriconazole/Emtricitabine	Interaction not studied.	
Voriconazole/Tenofovir disoproxil fumarate	Interaction not studied.	
Antimalarials		
Atovaquone and proguanil hydrochloride/Efavirenz (250/100 mg single dose/600 mg q.d.)	Atovaquone: AUC: ↓ 75% (↓ 62 to ↓ 84) C_{max}: ↓ 44% (↓ 20 to ↓ 61) Proguanil: AUC: ↓ 43% (↓ 7 to ↓ 65) C_{max}: ↔	Concomitant administration of atovaquone/proguanil with Vonavir should be avoided whenever possible.
Atovaquone and proguanil hydrochloride/Emtricitabine	Interaction not studied.	
Atovaquone and proguanil hydrochloride/Tenofovir disoproxil fumarate	Interaction not studied.	
ANTICONVULSANTS		
Carbamazepine/Efavirenz	Carbamazepine:	No dose

(400 mg q.d./600 mg q.d.)	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.	recommendation can be made for the use of Vonavir 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	When Vonavir is co-administered with an anticonvulsant that is a substrate of CYP450

	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.	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.	Vonavir 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.	Vonavir and vigabatrin or gabapentin can be co-administered without dose adjustment.

Vigabatrin/Emtricitabine Gabapentin/Emtricitabine	Interaction not studied.	
Vigabatrin/Tenofovir disoproxil fumarate Gabapentin/Tenofovir disoproxil fumarate	Interaction not studied.	
ANTICOAGULANTS		
Warfarin/Efavirenz Acenocoumarol/Efavirenz	Interaction not studied. Plasma concentrations and effects of warfarin or acenocoumarol are potentially increased or decreased by efavirenz.	Dose adjustment of warfarin or acenocoumarol may be required when co-administered with Vonavir.
ANTIDEPRESSANTS		
Selective Serotonin Reuptake Inhibitors (SSRIs)		
Sertraline/Efavirenz (50 mg q.d./600 mg 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 Vonavir, sertraline dose increases should be guided by clinical response.
Sertraline/Emtricitabine	Interaction not	

	studied.	
Sertraline/Tenofovir disoproxil fumarate	Interaction not studied.	
Paroxetine/Efavirenz (20 mg q.d./600 mg q.d.)	Paroxetine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔	Vonavir 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.	Vonavir and fluoxetine can be co-administered without dose adjustment.
Fluoxetine/Emtricitabine	Interaction not studied.	
Fluoxetine/Tenofovir disoproxil fumarate	Interaction not studied.	
Norepinephrine and dopamine reuptake inhibitor		

Bupropion/Efavirenz [150 mg single dose (sustained release)/600 mg q.d.]	Bupropion: AUC: ↓ 55% (↓ 48 to ↓ 62) C_{max}: ↓ 34% (↓ 21 to ↓ 47) Hydroxybupropion: AUC: ↔ C_{max}: ↑ 50% (↑ 20 to ↑ 80) (CYP2B6 induction)	Increases in bupropion dosage should be guided by clinical response, but the maximum recommended dose of bupropion should not be exceeded. No dose adjustment is necessary for efavirenz.
Bupropion/Emtricitabine	Interaction not studied.	
Bupropion/Tenofovir disoproxil fumarate	Interaction not studied.	
CARDIOVASCULAR AGENTS		
Calcium Channel Blockers		
Diltiazem/Efavirenz (240 mg q.d./600 mg q.d.)	Diltiazem: AUC: ↓ 69% (↓ 55 to ↓ 79) C_{max}: ↓ 60% (↓ 50 to ↓ 68) C_{min}: ↓ 63% (↓ 44 to ↓ 75) Desacetyl diltiazem: AUC: ↓ 75% (↓ 59 to ↓ 84) C_{max}: ↓ 64% (↓ 57 to ↓ 69)	Dose adjustments of diltiazem when co-administered with Vonavir should be guided by clinical response (refer to the Summary of Product Characteristics for diltiazem).

	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.	
Diltiazem/Emtricitabine	Interaction not studied.	
Diltiazem/Tenofovir disoproxil fumarate	Interaction not studied.	
Verapamil, Felodipine, Nifedipine and Nicardipine	Interaction not studied with efavirenz, emtricitabine, or	Dose adjustments of calcium channel blockers when co-administered with

	tenofovir disoproxil fumarate. When efavirenz is co-administered 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.	Vonavir should be guided by clinical response (refer to the Summary of Product Characteristics for the calcium channel blocker).
LIPID LOWERING MEDICINAL PRODUCTS		
HMG Co-A Reductase Inhibitors		
Atorvastatin/Efavirenz (10 mg q.d./600 mg q.d.)	Atorvastatin: AUC: ↓ 43% (↓ 34 to ↓ 50) C_{max}: ↓ 12% (↓ 1 to ↓ 26) 2-hydroxy atorvastatin: AUC: ↓ 35% (↓ 13 to ↓ 40) C_{max}: ↓ 13% (↓ 0 to ↓ 23) 4-hydroxy atorvastatin: AUC: ↓ 4% (↓ 0 to ↓ 31) C_{max}: ↓ 47% (↓ 9 to ↓ 51) Total active HMG	Cholesterol levels should be periodically monitored. Dosage adjustments of atorvastatin may be required when co-administered with Vonavir (refer to the Summary of Product Characteristics for atorvastatin).

	Co-A reductase inhibitors: AUC: ↓ 34% (↓ 21 to ↓ 41) C_{max}: ↓ 20% (↓ 2 to ↓ 26)	
Atorvastatin/Emtricitabine	Interaction not studied.	
Atorvastatin/Tenofovir disoproxil fumarate	Interaction not studied.	
Pravastatin/Efavirenz (40 mg q.d./600 mg q.d.)	Pravastatin: AUC: ↓ 40% (↓ 26 to ↓ 57) C_{max}: ↓ 18% (↓ 59 to ↑ 12)	Cholesterol levels should be periodically monitored. Dosage adjustments of pravastatin may be required when co-administered with Vonavir (refer to the Summary of Product Characteristics for pravastatin).
Pravastatin/Emtricitabine	Interaction not studied.	
Pravastatin/Tenofovir disoproxil fumarate	Interaction not studied.	
Simvastatin/Efavirenz (40 mg q.d./600 mg q.d.)	Simvastatin: AUC: ↓ 69% (↓ 62 to ↓ 73) C_{max}: ↓ 76% (↓ 63 to ↓ 79) Simvastatin acid: AUC: ↓ 58% (↓ 39 to ↓ 68) C_{max}: ↓ 51% (↓ 32 to ↓ 58) Total active HMG	Cholesterol levels should be periodically monitored. Dosage adjustments of simvastatin may be required when co-administered with Vonavir (refer to the Summary of Product Characteristics for simvastatin).

	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.	Vonavir 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	Ethinyloestradiol: AUC: ↔	A reliable method of barrier contraception must be used in

(0.035 mg+0.25 mg q.d./600 mg q.d.)	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.	addition to hormonal contraceptives (see section 4.6).
Ethinyloestradiol/Tenofovir disoproxil fumarate (-/300 mg q.d.)	Ethinyloestradiol: AUC: ↔	

	C_{max}: ↔ Tenofovir: AUC: ↔ C_{max}: ↔	
Norgestimate/Ethinyloestradiol/ Emtricitabine	Interaction not studied.	
Injection: Depomedroxyprogesterone acetate (DMPA)/Efavirenz (150 mg IM single dose DMPA)	In a 3-month 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 (see section 4.6).
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.	A reliable method of barrier contraception must be used in addition to hormonal contraceptives (see section 4.6).
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 Vonavir.
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 mg q.d./600 mg q.d.)	Methadone: AUC: ↓ 52% (↓ 33 to ↓ 66) C_{max}: ↓ 45% (↓ 25 to ↓ 59) (CYP3A4 induction) In a study of HIV infected intravenous 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 Vonavir concomitantly should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.
Methadone/Tenofovir disoproxil fumarate	Methadone:	

(40-110 mg q.d./300 mg q.d.)	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 Vonavir.
Buprenorphine/naloxone/Emtricitabine	Interaction not studied.	
Buprenorphine/naloxone/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, fosamprenavir/ritonavir, lorazepam, nelfinavir, zidovudine, aluminium/magnesium hydroxide antacids, famotidine or fluconazole. The potential for interactions with efavirenz and other azole antifungals, such as ketoconazole, has not been studied.

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential (see below and section 5.3)

Pregnancy should be avoided in women receiving Vonavir. Women of childbearing potential should undergo pregnancy testing before initiation of Vonavir.

Contraception in males and females

Barrier contraception should always be used in combination with other methods of contraception (for example, oral or other hormonal contraceptives, see section 4.5) while on therapy with Vonavir. Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of Vonavir 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 (see section 5.3).

Emtricitabine and tenofovir disoproxil fumarate: A moderate amount of data on pregnant women (between 300-1,000 pregnancy outcomes) indicates 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 (see section 5.3).

Vonavir 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 is excreted in milk; concentrations of efavirenz were much higher than those in maternal plasma. A risk to the infants cannot be excluded. Therefore Vonavir 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 Vonavir are available. Animal studies do not indicate harmful effects of efavirenz, emtricitabine or tenofovir disoproxil fumarate on fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, dizziness has been reported during treatment with efavirenz, emtricitabine and tenofovir disoproxil 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.

4.8 Undesirable effects

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 Vonavir (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 Vonavir 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 Vonavir (see section 4.4).

Discontinuation of Vonavir therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis (see section 4.4).

The administration of Vonavir with food may increase efavirenz exposure and may lead to an increase in the frequency of adverse reactions (see sections 4.4 and 5.2).

Tabulated list of adverse reactions

The adverse reactions from clinical study and post-marketing experience with Vonavir and the individual components of Vonavir in antiretroviral combination therapy are listed in Table 2 below by body system organ class, frequency and the component(s) of Vonavir 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 Vonavir: Treatment-emergent adverse reactions considered possibly or probably related to Vonavir reported in study AI266073 (over 48 weeks; n = 203), which have not been associated with one of the individual components of Vonavir, include:

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

Table 2: Adverse reactions associated with Vonavir listed by the component(s) of Vonavir to which the adverse reactions are attributable

	Vonavir		
	Efavirenz	**Emtricitabine**	**Tenofovir disoproxil fumarate**
Blood and lymphatic system disorders:			
Common		neutropenia	
Uncommon		anaemia[1]	

Immune system disorders:			
Common		allergic reaction	
Uncommon	hypersensitivity		
Metabolism and nutrition disorders:			
Very common			hypophosphataemia[2]
Common	hypertriglyceridaemia[3]	hyperglycaemia, hypertriglyceridaemia	
Uncommon	hypercholesterolaemia[3]		hypokalaemia[2]
Rare			lactic acidosis[3]
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]		
Nervous system disorders:			
Very common		headache	dizziness
Common	cerebellar coordination and balance disturbances[3], somnolence (2.0%)[3], headache (5.7%)[3], disturbance in attention (3.6%)[3], dizziness (8.5%)[3]	dizziness	headache

Uncommon	convulsions[3], amnesia[3], thinking abnormal[3], ataxia[3], coordination abnormal[3], agitation[3], tremor		
Eye disorders:			
Uncommon	vision blurred		
Ear and labyrinth disorders:			
Uncommon	tinnitus, vertigo		
Vascular disorders:			
Uncommon	flushing		
Gastrointestinal disorders:			
Very common		diarrhoea, nausea	diarrhoea, vomiting, nausea
Common	diarrhoea, vomiting, abdominal pain, nausea	elevated amylase including elevated pancreatic amylase, elevated serum lipase, vomiting, abdominal pain, dyspepsia	abdominal pain, abdominal distension, flatulence
Uncommon	pancreatitis		pancreatitis[3]
Hepatobiliary disorders:			
Common	elevated aspartate aminotransferase (AST), elevated alanine aminotransferase (ALT), elevated gamma-glutamyltransferase (GGT)	elevated serum AST and/or elevated serum ALT, hyperbilirubinaemia	increased transaminases
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
Musculoskeletal and connective tissue disorders:			
Very common		elevated creatine kinase	
Uncommon			rhabdomyolysis[2], muscular weakness[2]
Rare			osteomalacia (manifested as bone pain and infrequently contributing to fractures)[2,4], myopathy[2]
Renal and urinary disorders:			
Uncommon			increased creatinine, proteinuria

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		
General disorders and administration site conditions:			
Very common			asthenia
Common	fatigue	pain, asthenia	

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

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

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

[4] This adverse reaction was identified through post-marketing surveillance for either efavirenz, emtricitabine or tenofovir disoproxil fumarate. The frequency category was estimated from a statistical calculation based on the total number of patients 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).

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. Vonavir can be reinitiated in patients interrupting therapy because of rash. Use of appropriate antihistamines and/or corticosteroids is recommended when Vonavir 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 Vonavir. 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 Vonavir is taken concomitantly with meals possibly due to increased efavirenz plasma levels (see section 5.2). Dosing at bedtime seems to improve the tolerability of these symptoms (see section 4.2).

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

Renal impairment: As Vonavir may cause renal damage, monitoring of renal function is recommended (see sections 4.4 and 4.8 Summary of the safety profile).

Interaction with didanosine: Co-administration of Vonavir and didanosine is not recommended as it results in a 40-60% increase in systemic exposure to didanosine that may increase the risk of didanosine-related adverse reactions (see section 4.5). Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported.

Lactic acidosis 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 (see section 4.4).

Lipids, lipodystrophy and metabolic abnormalities: CART has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see section 4.4).

CART 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) (see section 4.4).

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

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

Paediatric population

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

Other special populations

Older people: Vonavir has not been studied in patients over the age of 65. Older people are more likely to have decreased hepatic or renal function, therefore caution should be exercised when treating older people with Vonavir (see section 4.2).

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 Vonavir (see sections 4.2, 4.4 and 5.2).

HIV/HBV or HCV co-infected patients: Only a limited number of patients were co-infected with HBV (n = 13) or HCV (n = 26) in study GS-01-934. The adverse reaction profile of efavirenz, emtricitabine and tenofovir disoproxil 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 (see section 4.4).

4.9 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 (see section 4.8), and standard supportive treatment applied as necessary.

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

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

5. Pharmacological properties

5.1 Pharmacodynamic properties

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

Mechanism of action and pharmacodynamic effects

Efavirenz is an NNRTI of HIV-1. Efavirenz non-competitively inhibits HIV-1 reverse transcriptase (RT) and does not significantly inhibit human immunodeficiency virus-2 (HIV-2) RT or cellular deoxyribonucleic acid (DNA) polymerases (α, β, γ, and δ). Emtricitabine is a nucleoside analogue of cytidine. Tenofovir disoproxil 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): Limited resistance data from patients treated with Vonavir 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 (Truvada) 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

	Efavirenz+ emtricitabine+ tenofovir disoproxil fumarate (N=244)		**Efavirenz+lamivudine/zidovudine (N=243)**	
Resistance analysis by week 144		19		31
On-therapy genotypes	19	(100%)	29	(100%)
Efavirenz resistance[1]	13	(68%)	21	(72%)
K103N	8	(42%)	18*	(62%)
K101E	3	(16%)	3	(10%)
G190A/S	2	(10.5%)	4	(14%)
Y188C/H	1	(5%)	2	(7%)
V108I	1	(5%)	1	(3%)
P225H	0		2	(7%)
M184V/I	2	(10.5%)	10*	(34.5%)
K65R	0		0	
TAMs[2]	0		2	(7%)

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

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

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

In the open-label extended phase of study GS-01-934, where patients received Vonavir on an empty stomach, 3 additional cases of resistance were seen. All 3 subjects had received a fixed dose combination of lamivudine and zidovudine (Combivir) and efavirenz for 144 weeks and then switched to Vonavir. Two subjects with confirmed virologic rebound developed NNRTI

resistance-associated substitutions to efavirenz including K103N, V106V/I/M and Y188Y/C reverse transcriptase substitutions at week 240 (96 weeks on Vonavir) and week 204 (60 weeks on Vonavir). A third subject had pre-existing NNRTI resistance-associated substitutions to efavirenz and the M184V reverse transcriptase resistance-associated substitution to emtricitabine at entry into the Vonavir extension phase and experienced a suboptimal virologic response, and developed K65K/R, S68N and K70K/E NRTI resistance-associated substitutions at week 180 (36 weeks on Vonavir).

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 Vonavir on an empty stomach. Data are available from 286 patients who switched to Vonavir: 160 had previously received efavirenz, emtricitabine and tenofovir disoproxil fumarate, and 126 had previously received Combivir and efavirenz. High rates of virologic suppression were maintained by subjects from both initial treatment groups who then received Vonavir in the open-label extended phase of the study. After 96 weeks of Vonavir treatment, HIV-1 RNA plasma concentrations remained < 50 copies/ml in 82% of patients and < 400 copies/ml in 85% of patients (intention to treat analysis (ITT), missing=failure).

Study AI266073 was a 48-week open-label randomised clinical study in HIV infected patients comparing the efficacy of Vonavir to antiretroviral therapy consisting of at least two nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) with a protease inhibitor or non-nucleoside reverse transcriptase inhibitor; however not a regimen containing all Vonavir components (efavirenz, emtricitabine and tenofovir disoproxil fumarate). Vonavir was administered on an empty stomach (see section 4.2). Patients had never experienced virological failure on a previous antiretroviral therapy, had no known HIV-1 mutations that confer resistance to any of the three components within Vonavir, and had been virologically suppressed for at least three months at baseline. Patients either changed to Vonavir (N=203) or continued on their original antiretroviral treatment regimen (N=97). Forty-eight week data showed that high levels of virologic suppression, comparable to the original treatment regimen, were maintained in patients who were randomised to change to Vonavir (see Table 4).

Table 4: 48-week efficacy data from study AI266073 in which Vonavir was administered to virologically suppressed patients on combination antiretroviral therapy

	Treatment group		
Endpoint	**Vonavir (N=203)** **n/N (%)**	**Stayed on original treatment regimen (N=97)** **n/N (%)**	**Difference between Vonavir 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 Vonavir [92.4% versus 94.0% for the PVR (sensitivity analysis) for Vonavir 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 Vonavir 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 Vonavir according to the type of prior antiretroviral regimen (Kaiser Permanente patient database)

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

No data are currently available from clinical studies with Vonavir in treatment-naïve patients or in heavily pretreated patients. There is no clinical experience with Vonavir 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 $\log_{10}$ reduction or 4 to 5 $\log_{10}$ reduction, respectively) (see section 4.4).

Paediatric population

The safety and efficacy of Vonavir in children under the age of 18 years have not been established.

5.2 Pharmacokinetic properties

The separate pharmaceutical forms of efavirenz, emtricitabine and tenofovir disoproxil fumarate were used to determine the pharmacokinetics of efavirenz, emtricitabine and tenofovir disoproxil fumarate, administered separately in HIV infected patients. The bioequivalence of one Vonavir 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)
$AUC_{0\text{-}last}$(ng·h/ml)	125,623.6 (25.7)	132,795.7 (27.0)	95.84 (90.73, 101.23)	10,682.6 (18.1)	10,874.4 (14.9)	97.98 (94.90, 101.16)	1,948.8 (32.9)	1,969.0 (32.8)	99.29 (91.02, 108.32)
AUC_{inf}(ng·h/ml)	146,074.9 (33.1)	155,518.6 (34.6)	95.87 (89.63, 102.55)	10,854.9 (17.9)	11,054.3 (14.9)	97.96 (94.86, 101.16)	2,314.0 (29.2)	2,319.4 (30.3)	100.45 (93.22, 108.23)
$T_{1/2}$ (h)	180.6 (45.3)	182.5 (38.3)		14.5 (53.8)	14.6 (47.8)		18.9 (20.8)	17.8 (22.6)	

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

Reference: single dose of a 600 mg efavirenz tablet, 200 mg emtricitabine capsule and 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

Vonavir 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 of tenofovir by 43.6% and 40.5%, and C_{max} by 16% and 13.5%, respectively without affecting emtricitabine exposures.

Vonavir is recommended for administration on an empty stomach since food may increase efavirenz exposure and may lead to an increase in the frequency of adverse reactions (see sections 4.4 and 4.8). It is anticipated that tenofovir exposure (AUC) will be approximately 30% lower following administration of Vonavir on an empty stomach as compared to the individual component tenofovir disoproxil fumarate when taken with food (see section 5.1).

Distribution

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

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

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

Biotransformation

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

There is limited metabolism of emtricitabine. The biotransformation of emtricitabine includes oxidation of the thiol moiety to form the 3'-sulphoxide diastereomers (approximately 9% of dose) and conjugation with glucuronic acid to form 2'-O-glucuronide (approximately 4% of dose). *In vitro* studies have determined that neither tenofovir disoproxil 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 kidneys by both filtration and an active tubular transport system with approximately 70 to 80% of the dose excreted unchanged in urine following intravenous administration. The apparent clearance of tenofovir averaged approximately 307 ml/min. Renal clearance has been estimated to be approximately 210 ml/min, which is in excess of the glomerular filtration rate. This indicates that active tubular secretion is an important part of the elimination of tenofovir.

Age

Pharmacokinetic studies have not been performed with efavirenz, emtricitabine or tenofovir in the older people (over 65 years of age).

Gender

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

Ethnicity

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

Paediatric population

Pharmacokinetic studies have not been performed with Vonavir in infants and children under 18 years of age (see section 4.2).

Renal impairment

The pharmacokinetics of efavirenz, emtricitabine and tenofovir disoproxil fumarate after co-administration of the separate pharmaceutical forms or as Vonavir 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.

Vonavir 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 (see sections 4.2 and 4.4).

Hepatic impairment

The pharmacokinetics of Vonavir have not been studied in HIV infected patients with hepatic impairment.Vonavir should be administered with caution to patients with mild hepatic impairment (see sections 4.3 and 4.4).

Vonavir must not be used in patients with severe hepatic impairment (see section 4.3) and is not recommended for patients with moderate hepatic impairment. In a single-dose study of efavirenz, half-life was doubled in the single patient with severe hepatic impairment (Child-Pugh-Turcotte Class C), indicating a potential for a much greater degree of accumulation. A multiple-dose study of efavirenz showed no significant effect on efavirenz pharmacokinetics in patients with mild hepatic impairment (Child-Pugh-Turcotte Class A) compared with controls. There were insufficient data to determine whether moderate or severe hepatic impairment (Child-Pugh-Turcotte Class B or C) affects efavirenz pharmacokinetics.

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

A single 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.

5.3 Preclinical safety data

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

Efavirenz was not mutagenic or clastogenic in conventional genotoxicity assays. Carcinogenicity studies showed an increased incidence of hepatic and pulmonary tumours in female mice, but not in male mice. The mechanism of tumour formation and the potential relevance for humans are not known. Carcinogenicity studies in male mice, male and female rats were negative.

Reproductive toxicity studies showed increased foetal resorptions in rats. No malformations were observed in foetuses from efavirenz-treated rats and rabbits. However, malformations were observed in 3 of 20 foetuses/newborns from efavirenz-treated cynomolgus monkeys given doses resulting in plasma efavirenz concentrations similar to those seen in humans. Anencephaly and unilateral anophthalmia with secondary enlargement of the tongue were observed in one foetus, microophthalmia was observed in another foetus and cleft palate was observed in a third foetus.

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

Tenofovir disoproxil 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.

6. Pharmaceutical particulars

6.1 List of excipients

Microcrystalline cellulose, Croscarmellose, Hydrocy propyl cellulose, Sodium lauryl sulphate, Magnesium Stearate , purified water, isopropyl Alcohol, Opadry White,

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

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

Store at Store at 20° to 25° C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F)

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle with a polypropylene child-resistant closure containing 30 film-coated tablets and silica gel desiccant.

6.6 Special precautions for disposal and other handling

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

7. Marketing authorisation holder

Emcure pharmaceuticals Ltd, India.

8. Marketing authorisation number(s)

Not available

9. Date of first authorisation/renewal of the authorisation

Not available

10. Date of revision of the text

Dec-2014