PROFESSIONAL INFORMATION FOR

TRENVIR

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TRENVIR 200 mg, 300 mg, 600 mg, film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains emtricitabine 200 mg, tenofovir disoproxil fumarate 300 mg and efavirenz 600 mg.

Sugar free.

For the full list of excipients, see **section 6.1.**

WARNING:

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION WITH OTHER ANTIRETROVIRALS (see section 4.4). 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 TRENVIR 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 TRENVIR TO ANY PATIENT (PARTICULARLY OBESE WOMEN) WITH HEPATOMEGALY, HEPATITIS OR OTHER KNOWN RISK FACTORS FOR LIVER DISEASE AND HEPATIC STEATOSIS (INCLUDING CERTAIN MEDICINES 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.

TRENVIR IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION AND THE SAFETY AND EFFICACY OF TRENVIR HAVE NOT BEEN ESTABLISHED IN PATIENTS CO-INFECTED WITH HBV AND HIV. SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO HAVE DISCONTINUED EMTRICITABINE (200 mg) OR TENOFOVIR, WHICH ARE COMPONENTS OF TRENVIR. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE TRENVIR AND ARE CO-INFECTED WITH HIV AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (see section 4.4).

3. PHARMACEUTICAL FORM

Film-coated tablets.

TRENVIR is a pink coloured, capsule-shaped, biconvex, film-coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TRENVIR is indicated for the treatment of HIV-1 infection in adults.

4.2 Posology and method of administration

Posology

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

A dose reduction and therapeutic drug monitoring should be considered in patients weighing less than 40 kg and presenting with long-term neuropsychiatric effects such as ataxia, encephalopathy, hyper-somnolence and coma.

Adults

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

Special populations

Elderly

Insufficient numbers of elderly patients have been evaluated in clinical studies of the components of TRENVIR to determine whether they respond differently than younger patients. Caution should be exercised when prescribing TRENVIR to the elderly, keeping in mind the greater frequency of decreased hepatic or renal function in these patients.

Renal impairment

TRENVIR is not recommended for patients with moderate to severe renal impairment (creatinine clearance < 50 mL/min). Patients with moderate or severe renal impairment require dose interval adjustments of emtricitabine and tenofovir that cannot be achieved with TRENVIR (see **section 4.3** and **4.4**).

Hepatic impairment

The pharmacokinetics of TRENVIR have not been studied in patients with hepatic impairment. Patients with mild to moderate liver disease (Child-Pugh-Turcotte Grade A or B) may be treated with the normal recommended dose of TRENVIR. Patients should be monitored carefully for adverse reactions, especially nervous system symptoms related to efavirenz.

If TRENVIR is discontinued in patients co-infected with HIV and HBV, these patients should be closely monitored for evidence of exacerbation of hepatitis.

Paediatric population

TRENVIR is not recommended for use in children below 18 years of age due to lack of data on safety and efficacy (see **section 4.3**).

Method of administration

It is recommended that TRENVIR be swallowed whole with water.

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

It is important to take TRENVIR on a regular dosing schedule to avoid missing doses. Patients should be told that if they forget to take TRENVIR, they should take the missed dose right away, unless it is less than 12 hours until the next day's dose. In this case, patients should be told not to take the missed dose and to take their next dose at the usual time.

Where discontinuation of therapy with one of the components of TRENVIR is indicated or where dose modification is necessary, separate preparations of efavirenz, emtricitabine and tenofovir are available. Please refer to the individual package inserts of these medicines.

If therapy with TRENVIR is discontinued, consideration should be given to the long half-life of efavirenz and long intracellular half-lives of tenofovir and emtricitabine. Because of interpatient variability in these parameters and concerns regarding development of resistance, HIV treatment guidelines should be consulted, also taking into consideration the reason for discontinuation.

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

Dose adjustment: If TRENVIR 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**).

4.3 Contraindications

TRENVIR is contraindicated in patients:

- with known hypersensitivity to emtricitabine, tenofovir or efavirenz or to any of the excipients in TRENVIR (see **section 6.1**).
- with moderate to severe renal impairment (creatine clearance < 50 mL/min) (see **section 4.2** and **4.4**).
- who are pregnant or breastfeeding (see **section 4.6**).
- who are concurrently receiving treatment with terfenadine, astemizole, bepridil, cisapride, midazolam, pimozide, triazolam or ergot derivatives (ergotamine, dihydroergotamine, ergonovine and methylergonovine), because competition for CYP3A4 by the efavirenz in TRENVIR could result in inhibition of the metabolism of these medicines and create the potential for serious and/or life-threatening adverse events (e.g. cardiac dysrhythmias, prolonged sedation or respiratory depression).
- younger than 18 years of age due to lack of data on safety and efficacy.

- with severe hepatic impairment (CPT, Class C).
- who are concurrently using voriconazole, since efavirenz significantly decreases voriconazole plasma concentrations, while voriconazole also significantly increases efavirenz plasma concentrations. Since TRENVIR is a fixed-dose combination product, the dose of efavirenz cannot be altered; therefore, voriconazole and TRENVIR must not be co-administered.
- who concomitantly take other medicines containing any of the components, efavirenz, emtricitabine or tenofovir, or who concomitantly take other cytidine analogues, such as lamivudine, and adefovir dipivoxil.
- 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.
- a history of previous liver injury/failure with efavirenz containing antiretroviral treatment.
- with a family history of sudden death or of congenital prolongation of the QTc interval on electrocardiograms, or with any other clinical condition known to prolong the QTc interval.
- with a history of symptomatic cardiac dysrhythmia or with clinically relevant bradycardia or with congestive cardiac failure accompanied by reduced left ventricle ejection fraction.
- with a severe disturbance of electrolyte balance e.g. hypokalaemia or hypomagnesemia.
- Co-administration with medicines that are known to prolong the QTc interval (prodysrhythmic):
    - *These medicines include:*
        - antidysrhythmics of classes IA and III,
        - neuroleptics, antidepressive medicines,
        - certain antibiotics including some medicines of the following classes: macrolides, fluoroquinolones, imidazole and triazole antifungal medicines,

- flecainide,
- certain antimalarials,
- methadone (see **sections 4.5**).

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

4.4 Special warnings and precautions for use

ALERT: Find out about medicines that should NOT be taken with TRENVIR (see **section 4.3**, **4.5** and **4.8**).

Serious nervous system and psychiatric symptoms have been reported with efavirenz, one of the active ingredients in TRENVIR.

Lactic acidosis* / hyperlactataemia / *Severe hepatomegaly with steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues, such as contained in TRENVIR, alone or in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering TRENVIR to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Patients with known risk factors for liver disease should only be given nucleoside analogues under cautious observation.

Use of TRENVIR can result in potentially fatal lactic acidosis as a consequence of mitochondrial dysfunction.

Clinical features are non-specific, and include nausea, vomiting, abdominal pain, dyspnoea, fatigue, and weight loss.

In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal < 2 mmol/L) and the serum bicarbonate and respond as follows:

- Lactate 2 to 5 mmol/L with minimum symptoms: switch to medicines that are less likely to cause lactic acidosis.
- Lactate 5 to 10 mmol/L with symptoms and/or with reduced standard bicarbonate: Stop Nucleotide reverse transcriptase inhibitors (NRTIs) and change treatment option. Once lactate has settled, use medicines that are less likely to cause lactic acidosis. Exclude other causes (e.g., sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis, and hyperthyroidism).
- Lactate > 10 mmol/L: STOP all therapy (80 % mortality).

The above lactate values may not be applicable to paediatric patients.

Any patient that develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations) should immediately cease TRENVIR treatment.

Patients with HIV and hepatitis B or C virus co-infection

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

Medical practitioners should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV). In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant professional information for these medicines. Patients co-infected with HIV and HBV who discontinue TRENVIR should be closely monitored with both clinical and laboratory follow-up for at least four months after stopping treatment.

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.

The safety and efficacy of efavirenz/emtricitabine/tenofovir disoproxil have not been studied for the treatment of chronic HBV infection. Emtricitabine and tenofovir individually and in combination have shown activity against HBV in pharmacodynamic studies (see **section 5.1**). Limited clinical experience suggests that emtricitabine and tenofovir disoproxil have an anti-HBV activity when used in antiretroviral combination therapy to control HIV infection.
Discontinuation of therapy in patients co-infected with HIV and HBV may be associated with severe, acute exacerbations of hepatitis.

Pancreatitis

Pancreatitis has been observed in some patients receiving TRENVIR. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of TRENVIR until diagnosis of pancreatitis is excluded.

Liver disease

Use of TRENVIR can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of TRENVIR have not been established in patients with significant underlying liver disorders/diseases. In case of concomitant antiviral therapy for hepatitis B or C, please also consult the relevant professional information for these medicines.
Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored. 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 in such patients,

temporary or permanent discontinuation of treatment must be considered.

TRENVIR is not recommended in patients with moderate to severe hepatic impairment because there are insufficient data to determine whether dose adjustments are required. Since efavirenz is principally metabolised by the CYP system, caution should be exercised in administering efavirenz/emtricitabine/tenofovir disoproxil to patients with mild hepatic impairment. These patients should be carefully monitored for efavirenz adverse reactions, especially nervous system symptoms. Laboratory tests should be performed to evaluate their liver disease at periodic intervals (see **section 4.2**).

The safety and efficacy of TRENVIR in patients with both HIV and hepatitis B virus infection have not been established.

Liver enzymes

In patients with known or suspected history of hepatitis B or C infection and in patients treated with other medicines associated with liver toxicity, monitoring of liver enzymes is recommended (see **section 4.4**, ***Patients Co-infected with HIV and HBV***). In patients with persistent elevations of serum transaminases to greater than 5 times the upper limit of the normal range, the benefit of continued therapy with TRENVIR needs to be weighed against the unknown risks of significant liver toxicity (see **section 4.8**).

Liver failure

There is some evidence that efavirenz is associated with three clinical pathological patterns of medicines induced liver failure in HIV positive patients of which the sub massive necrosis histological pattern seems to be associated with a high morbidity/mortality risk and may present many months after therapy has been initiated or even stopped. Risk factors include younger age, CD4+ counts > 350 cells/µL and female gender.

Patients on TRENVIR or efavirenz containing antiretroviral treatment (ART) should be regularly

monitored for jaundice (including a laboratory bilirubin and liver enzymes) and bleeding tendencies.

Early detection and treatment of the liver failure and the immediate discontinuation of TRENVIR or efavirenz containing medicines should be stressed. Patients who discontinued treatment with TRENVIR should be followed up for symptoms/signs of liver failure for up to 12 months.

TRENVIR is not recommended in patients with moderate to severe hepatic impairment because there are insufficient data to determine whether dose adjustments are required.

Co-administration with related medicines

Related medicines not for co-administration with TRENVIR include tenofovir DF, emtricitabine, emtricitabine/tenofovir DF and efavirenz, which contain the same active ingredients as TRENVIR. TRENVIR 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 between emtricitabine and lamivudine, TRENVIR should not be co-administered with medicines containing lamivudine, including lamivudine/zidovudine, lamivudine, abacavir sulphate/lamivudine or abacavir sulphate/lamivudine/zidovudine. Since emtricitabine and tenofovir are primarily eliminated by the kidneys, co-administration of TRENVIR with medicines that reduce renal function or compete for active tubular secretion may increase serum concentrations of emtricitabine, tenofovir, and/or other renally eliminated medicines. Some examples include, but are not limited to adefovir dipivoxil, cidofovir, acyclovir, valaciclovir, ganciclovir and valganciclovir. TRENVIR should not be administered concomitantly with adefovir dipivoxil. Co-administration, of TRENVIR 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 reaction. Rarely, pancreatitis and lactic acidosis, sometimes fatal have been reported.

Co-administration with other medicinal products

Concomitant use of TRENVIR and St. John's wort (*Hypericum perforatum*) or St. John's wort-containing products is not recommended. Co-administration of NNRTIs, including efavirenz, with St. John's wort is expected to substantially decrease NNRTI concentrations and may result in suboptimal levels of efavirenz and lead to loss of virologic response and possible resistance to efavirenz or to the class of NNRTIs.

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

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

Opportunistic infections

Patients receiving TRENVIR 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 health care providers experienced in the treatment of patients with HIV associated diseases. Regular monitoring of viral load and CD4 counts needs to be done.

The risk of HIV transmission to others

Patients should be advised that current antiretroviral therapy, including TRENVIR, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Effect of food

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

Cholesterol

Monitoring of cholesterol and triglycerides should be considered in patients treated with TRENVIR (see **section 4.8**).

QTc Prolongation

QTc prolongation has been observed with the use of efavirenz (see **sections 4.3** and **4.5**). For patients at increased risk of Torsade de Pointes or who are receiving medicinal products with a known risk for Torsade de Pointes, the administration of TRENVIR is contraindicated (see **section 4.3**) or consider alternatives to TRENVIR.

Psychiatric Symptoms

There have been reports of patients treated with efavirenz, which is a component of TRENVIR, experiencing serious side effects such as severe depression, psychosis or suicidal ideation, catatonia, suicide attempts, aggressive behaviour, paranoid reactions, and manic reactions.

Although efavirenz was associated with an increase in these psychiatric experiences, there are other associated factors such as a history of injection medicine use, psychiatric history, and the use of psychiatric medication. Other adverse events such as death by suicide, psychosis like behaviour and delusions have been reported.

Patients with serious psychiatric adverse experiences should seek immediate medical evaluation to assess the possibility that the symptoms may be related to the use of efavirenz, and if so, to determine whether the risks of continued therapy outweigh the benefits (see **section 4.8**).

Nervous system symptoms

Patients receiving TRENVIR should be alerted to the potential for additive central nervous system effects when TRENVIR is used concomitantly with alcohol or psychoactive medicines. Patients who experience central nervous system symptoms such as dizziness, impaired concentration, and/or drowsiness should avoid potentially hazardous tasks such as driving or operating machinery.

Nervous system symptoms have been reported with efavirenz use (see **section 4.8**). In addition, there have been reports of psychosis-like reactions, such as delusions and inappropriate behaviour (including aggressive reactions), predominantly in patients with a history of mental illness or substance abuse. Severe acute depression (including suicidal ideation/attempts) has also been infrequently reported in both efavirenz-treated and control-treated patients, particularly in patients with a previous history of depression.

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. 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. Dosing at bedtime may improve the tolerability of these nervous system symptoms (see **sections 4.2** and **4.8**).

Patients should be advised that if they experience these symptoms, they should contact their doctor immediately because discontinuation of TRENVIR may be required.

Convulsions

Convulsions have been observed in patients receiving efavirenz, generally in the presence of a known medical history of seizures. Caution must be taken in any patient with a history of seizures. Patients who are receiving concomitant anticonvulsant medicines primarily metabolised by the liver, such as carbamazepine, phenytoin, and phenobarbital, may require periodic monitoring of plasma levels (see **section 4.5**).

In a drug-interaction study, carbamazepine plasma concentrations were decreased when carbamazepine was co-administered with efavirenz (see **section 4.5**).

Renal impairment **(see section 4.3)**

Emtricitabine and tenofovir, two of the active ingredients in TRENVIR, are principally eliminated by the kidney however efavirenz is not. Dosing interval adjustment of emtricitabine and tenofovir is recommended in all patients with creatinine clearance 30 to 49 mL/min. Since this is not possible with a fixed dose combination, TRENVIR should not be administered to patients with creatinine clearance < 50 mL/min or patients requiring haemodialysis (see **section 4.2**).

$$\text{CrCl (mL/min)} = \frac{140 - \text{age (years)} \times \text{weight (kg)} \; [\times 0{,}85 \text{ if female}]}{72 \times \text{serum creatinine (mg/dL)}}$$

Renal impairment, including cases of acute renal failure, elevated creatinine, hypophosphatemia and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported in association with the use of tenofovir (see **section 4.8**). The majority of these cases occurred in patients with underlying systemic or renal disease, or in patients taking nephrotoxic medicines. However, some cases occurred in patients without identifiable risk factors.

TRENVIR should be avoided with concurrent or recent use of nephrotoxic medicines (e.g., aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir, interleukin 2). Patients at risk for, or with a history of, renal dysfunction and patients receiving concomitant nephrotoxic medicines is unavoidable, renal function should be carefully monitored for changes in serum creatinine and phosphorus weekly (see **section 4.5**).

Cases of acute renal failure after initiation of high dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs) have been reported in patients treated with tenofovir disoproxil and with risk factors for renal dysfunction. If TRENVIR is co-administered with an NSAID, renal function should be monitored adequately.

Renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir disoproxil in clinical practice (see **section 4.8**).

It is recommended that creatinine clearance is calculated in all patients prior to initiating therapy with TRENVIR and renal function (creatinine clearance and serum phosphate) is also monitored after two to four weeks of treatment, after three months of treatment and every three to six months thereafter in patients without renal risk factors. In patients with a history of renal dysfunction or in patient who are at risk of renal dysfunction, a more frequent monitoring of renal function is required. If serum phosphate is < 1,5 mg/dL (0,48 mmol/L) or creatinine clearance is decreased to < 50 mL/min in any patient receiving TRENVIR, 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 TRENVIR is a combination product and the dosing interval of the individual components cannot be altered, treatment with TRENVIR must be interrupted in patients with confirmed creatinine clearance < 50 mL/min or decreases in serum phosphate to < 1,0 mg/dL (0,32 mmol/L). Interrupting treatment with TRENVIR should also be considered in case of progressive decline of renal function when no

other cause has been identified. Where discontinuation of therapy with one of the components of TRENVIR is indicated or where dose modification is necessary, separate preparations of efavirenz, emtricitabine and tenofovir disoproxil fumarate are available.

Skin reactions

Mild to moderate rash has been reported with the individual components of TRENVIR. 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 %.

TRENVIR 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 medicines of the NNRTI class is limited. TRENVIR is not recommended for patients who have had a life-threatening cutaneous reaction (e.g. Stevens-Johnson syndrome) while taking an NNRTI.

Weight and metabolic parameters

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

Mitochondrial dysfunction

Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. These damages are most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV negative infants exposed *in utero* and/or postnatally to nucleoside analogues these have predominantly concerned treatment with regimens containing zidovudine. Apart from lactic acidosis/hyperlactataemia/hyperlipasemia (see above) other manifestations of mitochondrial dysfunction include haematological disorders (anaemia, neutropenia) and peripheral neuropathy. Late onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour), whether they are transient or permanent is currently unknown. Any foetus 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.

Osteonecrosis

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

Patients with HIV-1 harbouring mutations

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

Reproductive risk potential

Efavirenz may cause foetal harm when administered during the first trimester to a pregnant woman. Pregnancy should be avoided in women receiving TRENVIR. Barrier contraception should always be used in combination with other methods of contraception (e.g. oral or other hormonal contraceptives). Women of childbearing potential should undergo pregnancy testing before initiation of TRENVIR. If this medicine is used during the first trimester of pregnancy, or if the patient becomes pregnant while taking this medicine, the patient should be apprised of the potential harm to the foetus.

There are no adequate and well-controlled studies of TRENVIR in pregnant women.

Bone effects

Tenofovir

In a 144 weeks controlled clinical study that compared tenofovir disoproxil with stavudine in combination with lamivudine and efavirenz in antiretroviral- naïve patients, small decreases from baseline in bone mineral density (BMD) were seen at the lumbar spine and hip in both treatment arms of the study. At week 144, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in patients who received tenofovir + lamivudine + efavirenz compared with patients who received stavudine + lamivudine + efavirenz. Changes in BMD at the hip were similar between the two treatment groups. In both groups, the majority of the reduction in BMD occurred in the first 24 to 48 weeks of the study and this reduction was sustained through week 144. Twenty-eight percent of tenofovir-treated patients versus 21 % of stavudine-treated patients lost at least 5 % of BMD at the spine or 7 % of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 patients in the tenofovir-group and 6 patients in the stavudine-group. In addition, there were significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide and urinary N-telopeptide) in the tenofovir-group relative to the stavudine-group, suggesting increased bone turnover. Serum parathyroid hormone levels and 1,25 vitamin D levels were also

higher in the tenofovir-group. Except for bone-specific alkaline phosphatase, these changes resulted in values that remained within the normal range. The effects of tenofovir-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. For additional information, please consult the tenofovir disoproxil fumarate professional information.

In other studies (prospective and cross-sectional), the most pronounced decreases in BMD were seen in patients treated with tenofovir disoproxil as part of a regimen containing a boosted protease inhibitor. Alternative treatment regimens should be considered for patients with osteoporosis that are at a high risk for fractures.

Bone abnormalities such as osteomalacia which can manifest as persistent or worsening bone pain, and which can infrequently contribute to fractures, may be associated with tenofovir disoproxil-induced proximal renal tubulopathy (see **section 4.8**).
Bone monitoring should be considered for HIV infected patients who have a history of pathologic bone fracture or are at risk for osteopenia. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected or detected, then appropriate consultation should be obtained.

Lipodystrophy and metabolic abnormalities

Combination antiretroviral therapy has been associated with the redistribution/accumulation of body fat, including central obesity, dorsocervical fat, enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and elevated serum lipid and glucose levels in HIV patients.
Clinical examination should include evaluation for physical signs of fat redistribution. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment**.**

Immune reconstitution inflammatory syndrome (IRIS)

IRIS is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination Anti-Retroviral Therapy (cART).

Typically, such reaction presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of an asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRIS usually develops within the first three months of initiation of cART and occurs more commonly in patients with low CD4 counts. Common examples of IRIS reactions to opportunistic diseases are tuberculosis, focal atypical mycobacterial infections, cytomegalovirus retinitis, cryptococcal meningitis and *Pneumocystis jirovecii* (*carinii*) pneumonia (PCP).

Appropriate treatment of the opportunistic disease should be instituted or continued, and cART continued. Inflammatory manifestations generally subside after a few weeks. Severe cases may respond to glucocorticoids, but there is only limited evidence for this in patients with tuberculosis IRIS. Autoimmune disorders (such as Graves' disease, polymyositis, Guillain-Barre Syndrome and autoimmune hepatitis) have also been reported as IRIS reactions; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Use in elderly

Clinical studies of efavirenz, emtricitabine or tenofovir DF did not include sufficient numbers of subjects aged 65 or over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly patients should be cautious, keeping in mind the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other medicine therapy.

Paediatric population

TRENVIR is not recommended for patients less than 18 years of age because it is a fixed-dose combination tablet containing a component, tenofovir DF, for which safety and efficacy have not been established in this age group (see **section 4.3**).

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 TRENVIR 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.

Late Onset Neurotoxicity

TRENVIR may cause long-term neuropsychiatric effects. Severe reversible ataxia, often with signs of encephalopathy, associated with supratherapeutic efavirenz concentrations were reported in underweight women (less than 40 kg) who were probably slow metabolisers.

Cases of efavirenz-induced hyper-somnolence resulting in coma and death and brain histology demonstrated by vacuolar axonopathy were reported.

Lower doses of TRENVIR and therapeutic drug monitoring should be considered in patients with body weight of less than 40 kg and patients presenting with severe and prolonged neuropsychiatric manifestations.

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.

4.5 Interaction with other medicines and other forms of interaction

General interactions

No interaction studies have been conducted using TRENVIR tablets. As TRENVIR contains efavirenz, emtricitabine and tenofovir, any interactions that have been identified with these medicines individually may occur with TRENVIR. Interaction studies with these medicines have only been performed in adults.

As a fixed combination, TRENVIR should not be administered concomitantly with other medicines containing any of the components, efavirenz, emtricitabine or tenofovir, concomitantly with other cytidine analogues, such as lamivudine and adefovir dipivoxil (see **section 4.3**).

TRENVIR should not be co-administered with products containing efavirenz unless needed for dose adjustment e.g. with rifampicin (see **section 4.2**).

TRENVIR 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**).

Emtricitabine and Tenofovir

The steady state pharmacokinetics of emtricitabine and tenofovir were unaffected when emtricitabine and tenofovir disoproxil fumarate were administered together versus each medicine dosed alone. No clinically significant interactions have been observed between emtricitabine, and famciclovir, indinavir, stavudine, tenofovir DF and zidovudine. Similarly, no clinically significant medicine interactions have been observed between tenofovir DF and abacavir, adefovir dipivoxil, efavirenz, emtricitabine, indinavir, lamivudine, lopinavir/ritonavir, methadone, nelfinavir, oral contraceptives, ribavirin, and saquinavir/ritonavir in studies conducted in healthy volunteers.

Co-administration of tenofovir disoproxil fumarate 300 mg once daily for 7 days with emtricitabine, 200 mg once daily for 7 days, caused no changes in the C_{max} or AUC of emtricitabine. However, C_{min} of emtricitabine increased by 20 % [90 % confidence interval (CI) + 12 % to + 29 %]. The C_{max}, AUC and C_{min} of tenofovir were unchanged.

In vitro and clinical pharmacokinetic medicines interaction studies have shown the potential for CYP450 mediated interactions involving emtricitabine and tenofovir, two of the active ingredients in TRENVIR, with other medicines is low.

Atazanavir and lopinavir/ritonavir have been shown to increase tenofovir concentrations. The mechanism of this interaction is unknown. Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders. Patients receiving either atazanavir or lopinavir/ritonavir with tenofovir disoproxil fumarate should be monitored for tenofovir-associated adverse events. TRENVIR should be discontinued in patients who develop tenofovir-associated adverse events (for atazanavir dosing adjustment recommendations, see **section 4.5**).

Emtricitabine and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. No medicine interactions due to competition for renal excretion have been observed; however, co-administration of TRENVIR with medicines that are eliminated by active tubular secretion may increase concentrations of emtricitabine, tenofovir and/or the co-administered medicine.

Medicines that decrease renal function may increase concentrations of emtricitabine and/or tenofovir. Some examples include, but are not limited to acyclovir, adefovir dipivoxil, cidofovir, ganciclovir, valacyclovir and valganciclovir.

Other important medicine interaction information for TRENVIR is summarized in Table 1 and Table 2. The medicine interactions described are based on studies conducted with efavirenz, emtricitabine or tenofovir DF as individual medicines or are potential medicine interactions, no

medicine interaction studies have been conducted using TRENVIR. The tables include potentially significant interactions but are not all inclusive.

Efavirenz

The efavirenz in TRENVIR with metamizole, is an inducer of CYP3A4, CYP2B6 and UGT1A1. Other compounds that are substrates of CYP3A4 may have decreased plasma concentrations when co-administered with TRENVIR. *In vitro* studies have demonstrated that efavirenz inhibits 2C9, 2C19 and 3A4 isozymes in the range of observed efavirenz plasma concentrations. Co-administration of efavirenz with medicines primarily metabolised by these isozymes may result in altered plasma concentrations of the co-administered medicine. Therefore, appropriate dose adjustments may be necessary for these medicines.

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. Medicines which induce CYP3A4 activity (e.g. phenobarbitone, rifampicin, rifabutin) would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations. 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**).

No clinically significant medicines interactions have been observed between tenofovir disoproxil fumarate, zidovudine, lamivudine, azithromycin, fluconazole, lorazepam, cetirizine, paroxetine and efavirenz. Concomitant administration of efavirenz 600 mg once daily for 14 days with tenofovir 300 mg once daily did not result in any changes in the C_{max}, C_{min} or AUC of either

efavirenz or tenofovir. Single doses of famotidine or an aluminium and magnesium antacid with simethicone had no effects on efavirenz exposures.

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

Abacavir

No clinically significant medicines interactions have been observed between tenofovir disoproxil fumarate, one of the active ingredients in TRENVIR, and abacavir. Co-administration of a single dose of abacavir 300 mg with tenofovir 300 mg caused no changes in the C_{max} or AUC of tenofovir. However, C_{max} of abacavir increased by 12 % (90 % CI - 1 % to + 26 %), while the AUC remained unchanged.

Adefovir dipivoxil

No clinically significant medicines interactions have been observed between tenofovir disoproxil fumarate, one of the active ingredients in TRENVIR and adefovir dipivoxil. Concomitant administration of a single dose of adefovir dipivoxil 10 mg with tenofovir 300 mg did not result in any changes in the C_{max}, C_{min} or AUC of tenofovir nor in the C_{max} or AUC of adefovir dipivoxil.

TRENVIR should not be administered concomitantly with adefovir dipivoxil due to the increased risk of renal toxicity.

Amprenavir

Co-administration of amprenavir/ritonavir and TRENVIR is not recommended, as efavirenz reduces the C_{max}, C_{min} and AUC of amprenavir by 40 %.

Atazanavir

Co-administration of atazanavir 400 mg once daily for 14 days with tenofovir 300 mg once daily resulted in a 14 % increase (90 % CI +8 % to +20 %) in tenofovir C_{max}, 24 % increase (+21 % to +28 %) in tenofovir AUC and 22 % increase (+15 % to +30 %) in tenofovir C_{min}. Corresponding parameters for atazanavir showed a 21 % decrease (-27 % to -14 %) in C_{max}, 25 % decrease (-30 % to -19 %) in AUC and 40 % decrease (-48 % to -32 %) in C_{min}. In HIV-infected patients, addition of tenofovir disoproxil fumarate to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and C_{min} values of atazanavir that were 2,3- and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone.

Co-administration of atazanavir/ritonavir with tenofovir resulted in increased exposure to tenofovir. Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders.

Co-administration of efavirenz with atazanavir in combination with low-dose ritonavir resulted in substantial decreases in atazanavir exposure due to CYP3A4 induction, necessitating dosage adjustment of atazanavir. Co-administration of efavirenz and atazanavir in combination with ritonavir may lead to increases in efavirenz exposure which may worsen the tolerability profile of efavirenz.

Insufficient data are available to make a dosing recommendation for atazanavir/ritonavir in combination with TRENVIR. Therefore, co-administration of atazanavir/ritonavir and TRENVIR is not recommended.

Calcium channel blockers

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. Dose adjustments of diltiazem and other calcium channel blockers (such as verapamil, felodipine, nifedipine and nicardipine) when co-administered with TRENVIR should be guided by clinical response.

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 and are therefore possible with TRENVIR administration. 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. Negative results were obtained when more specific confirmatory testing was performed with gas chromatography/mass spectrometry.

Carbamazepine

Co-administration of carbamazepine with efavirenz decreased carbamazepine AUC, C_{max} and C_{min} with 27 % (90 % CI - 20 % to - 3 %), 20 % (-15 % to - 24 %), and 35 % (- 24 % to - 44 %), respectively, due to CYP3A4 induction. Corresponding decreases in efavirenz AUC, C_{max} and C_{min} (due to CYP3A4 and CYP2B6 induction) were 36 % (- 32 % to - 40 %), 21 % (-15 % to - 26 %), and 47 % (-41 % to -53 %), respectively. No dose recommendation can be made for the use of TRENVIR with carbamazepine. An alternative anticonvulsant should be considered. Carbamazepine plasma levels should be monitored periodically.

Clarithromycin

Co-administration of 400 mg of efavirenz once daily with clarithromycin given as 500 mg every 12 hours for seven days resulted in a significant effect of efavirenz on the pharmacokinetics of clarithromycin. The AUC and C_{max} of clarithromycin decreased 39 % and 26 %, respectively, while the AUC and C_{max} of the active clarithromycin hydroxy metabolite were increased 34 % and 49 %, respectively, when used in combination with efavirenz. The clinical significance of these changes in clarithromycin plasma levels is not known. In uninfected volunteers 46 % developed rash while receiving efavirenz and clarithromycin. No dose adjustment of efavirenz is recommended when given with clarithromycin. Alternatives to clarithromycin may be considered.

Other macrolide antibiotics, such as erythromycin, have not been studied in combination with TRENVIR.

Didanosine

Concomitant administration of a single dose of enteric-coated didanosine 400 mg with tenofovir 300 mg did not result in any changes in the C_{max}, C_{min} or AUC of tenofovir. The same holds true for the combination of buffered didanosine 250 or 400 mg once daily for 7 days with tenofovir 300 mg once daily.

When administered with multiple doses of tenofovir, the C_{max} and AUC of didanosine 400 mg increased significantly. The mechanism of this interaction is unknown. When didanosine 250 mg enteric-coated capsules were administered with tenofovir systemic exposures to didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions.

For a detailed summary of the changes in pharmacokinetic parameters for didanosine, please refer to the table below.

Table 1: ***Medicine interactions: Pharmacokinetic parameters for didanosine in the presence of tenofovir as in TRENVIR.***

Didanosine dose	Tenofovir method of	N	% Difference (90 % CI) vs.

(mg)/ Method of administration[1]	administration[1]		didanosine 400 mg alone, fasted[2]	
			C_{max}	AUC
Buffered tablets				
400 once daily[3] X 7 days	Fasted 1 hour after didanosine	14	↑28 (↑11 - ↑48)	↑44 (↑31 - ↑59)
Enteric-coated tablets				
400 once, fasted	With food, 2 hr after didanosine	26	↑48 (↑25 - ↑76)	↑48 (↑31 - ↑67)
400 once, with food	Simultaneously with didanosine	26	↑64 (↑41 - ↑89)	↑60 (↑44 - ↑79)
250 once, fasted	With food, 2 hr after didanosine	28	↓10 (↓22 - ↑3)	↔
250 once, fasted	Simultaneously with didanosine	28	↔	↑14 (0 - ↑31)
250 once, with food	Simultaneously with didanosine	28	↓29 (↓39 - ↓18)	↓11 (↓23 - ↑2)

1. Administration with food was with a light meal.
2. ↑ = increase; ↓ = decrease; ↔ = no difference.
3. Includes 4 subjects weighing < 60 kg receiving ddL 250 mg.

Co-administration of tenofovir disoproxil fumarate and didanosine results in a 40 % to 60 % increase in systemic exposure to didanosine that may increase the risk for didanosine-related adverse events. Cases of pancreatitis and lactic acidosis, sometimes fatal, have been reported. Co-administration of tenofovir disoproxil fumarate and didanosine at a dose of 400 mg daily has been associated with a significant decrease in CD4 cell count, possibly due to an intracellular interaction increasing phosphorylated (i.e. active) didanosine. A decreased dosage of 250 mg didanosine co-administered with tenofovir disoproxil fumarate therapy has been associated with reports of high rates of virologic failure within several tested combinations. Co-administration of TRENVIR and didanosine is not recommended.

Famciclovir

No clinically significant medicine interactions have been observed between emtricitabine, one of the active ingredients in TRENVIR, and famciclovir. Co-administration of single doses of

famciclovir 500 mg with a single dose of emtricitabine 200 mg did not alter the C_{max} or AUC of emtricitabine or famciclovir.

HMG Co-A reductase inhibitors

Co-administration of efavirenz with HMG Co-A reductase inhibitors, such as atorvastatin and pravastatin, led to decreases in the AUC and C_{max} of the HMG Co-A reductase inhibitors and their active metabolites. Cholesterol levels should be periodically monitored when atorvastatin, pravastatin or simvastatin is co-administered with TRENVIR. Dosage adjustments of statins may be required.

Immunosuppressants

Co-administration of tacrolimus with emtricitabine or tenofovir disoproxil fumarate did not result in any changes in the AUC, C_{max} or C_{min} of tacrolimus, emtricitabine or tenofovir disoproxil fumarate. Although the interaction between efavirenz and tacrolimus has not been studied, decreased exposure of tacrolimus may be expected due to CYP3A4 induction. Tacrolimus is not anticipated to impact exposure of efavirenz. Dose adjustments of tacrolimus may be required. Close monitoring of tacrolimus concentrations for at least two weeks (until stable concentrations are reached) is recommended when starting or stopping treatment with TRENVIR.

Indinavir

No clinically significant medicines interactions have been observed between the emtricitabine in TRENVIR and indinavir. Co-administration of single doses of indinavir 800 mg with a single dose of emtricitabine 200 mg did not alter the C_{max} or AUC of emtricitabine or indinavir.

Similarly, no clinically significant medicines interactions have been observed between tenofovir disoproxil fumarate, one of the active ingredients in TRENVIR, and indinavir. There was a 14 %

increase (90 % CI - 3 % to + 33 %) in the C_{max} of tenofovir when indinavir 800 mg three times daily for 7 days, was co-administered with tenofovir 300 mg once daily. The C_{min} and AUC of tenofovir remained unchanged as did the C_{min} and AUC of indinavir. Indinavir C_{max} decreased by 11 % (- 30 % to + 12 %).

When indinavir (800 mg every 8 hours) was given with efavirenz (200 mg every 24 hours), the indinavir AUC and C_{trough} were decreased by approximately 31 % and 16 %, respectively, as a result of enzyme induction.

Insufficient data are available to make a dosing recommendation for indinavir when dosed with TRENVIR. 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 TRENVIR and indinavir.

Itraconazole

Co-administration of itraconazole and efavirenz resulted in decreased itraconazole AUC, C_{max} and C_{min} due to CYP3A4 induction. No dose recommendations can be made for the use of TRENVIR in combination with itraconazole. An alternative antifungal treatment should be considered.

Interaction studies with TRENVIR and ketoconazole have not been conducted. Efavirenz has the potential to decrease plasma concentrations of ketoconazole.

Lamivudine

No clinically significant medicines interactions have been observed between the tenofovir disoproxil fumarate in TRENVIR and lamivudine. Co-administration of lamivudine 150 mg twice daily for 7 days with tenofovir 300 mg once daily did not result in any changes in the C_{max}, C_{min} or

AUC of tenofovir. While the C_{min} and AUC of lamivudine were unchanged, the C_{max} decreased by 24 % (- 34 % to - 12 %).

Due to similarities with emtricitabine, TRENVIR should not be administered concomitantly with other cytidine analogues, such as lamivudine.

Lopinavir/Ritonavir

No clinically significant medicine interactions have been observed between tenofovir disoproxil fumarate, one of the active ingredients in TRENVIR, and lopinavir/ritonavir. Co-administration of a combination of lopinavir 400 mg and ritonavir 100 mg twice daily for 14 days with tenofovir 300 mg once daily resulted in a 32 % increase (90 % CI + 26 % to + 38 %) in tenofovir AUC and 29 % increase (+ 23 % to + 66 %) in tenofovir C_{min}, while tenofovir C_{max} remained unchanged. There were no changes in C_{max}, C_{min} or AUC of lopinavir and ritonavir. Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders.

When efavirenz 600 mg (given once daily at bedtime) and ritonavir 500 mg (given every 12 hours) were studied in infected volunteers, the combination was not well tolerated and was associated with a higher frequency of adverse clinical experiences (for example, dizziness, nausea, paraesthesia, and elevated liver enzymes occurred). Monitoring of liver enzymes is recommended when efavirenz is used in combination with ritonavir.

Co-administration of lopinavir/ritonavir with efavirenz resulted in a substantial decrease in lopinavir exposure, necessitating dosage adjustment of lopinavir/ritonavir.

Insufficient data are available to make a dosing recommendation for lopinavir/ritonavir when dosed with TRENVIR. Co-administration of lopinavir/ritonavir and TRENVIR is not recommended.

Methadone

No clinically significant medicines interactions have been observed between the tenofovir disoproxil fumarate in TRENVIR and methadone. Following multiple dosing to HIV-negative subjects receiving chronic methadone maintenance therapy, steady state tenofovir pharmacokinetics were similar to those observed in previous studies, indicating lack of clinically significant medicines interactions between methadone and the tenofovir in TRENVIR.

Specifically, when methadone 40 to 110 mg once daily for 14 days was co-administered with tenofovir 300 mg once daily, R-(active), S- and total methadone exposures were equivalent when dosed alone or with tenofovir. Individual subjects were maintained on their stable methadone dose. No pharmacodynamic alterations (opiate toxicity or withdrawal signs or symptoms) were reported.

However, co-administration of efavirenz with methadone, in HIV-infected IV medicine users, 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 should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.

Oral contraceptives

No clinically significant medicine interactions have been observed between the tenofovir disoproxil fumarate in TRENVIR and oral contraceptives.

Following multiple dosing to HIV-negative subjects receiving oral contraceptives, steady state tenofovir pharmacokinetics were similar to those observed in previous studies, indicating lack of

clinically significant medicines interactions between these medicines and the tenofovir in TRENVIR.

In terms of possible interactions with efavirenz, only the ethinyloestradiol component of oral contraceptives has been studied. The AUC following a single dose of ethinyloestradiol was increased (37 %) after multiple dosing of efavirenz. No significant changes were observed in C_{max} of ethinyloestradiol. The clinical significance of these effects is not known. No effect of a single dose of ethinyloestradiol on efavirenz C_{max} or AUC was observed. Because the potential interaction of TRENVIR with oral contraceptives has not been fully characterised, a reliable method of barrier contraception must be used in addition to oral contraceptives.

Phenytoin, phenobarbital, and other anticonvulsants

There is a potential for reduction or increase in the plasma concentrations of phenytoin, phenobarbital and other anticonvulsants that are substrates of CYP450 isoenzymes with efavirenz. When TRENVIR is co-administered with an anticonvulsant that is a substrate of CYP450 isoenzymes, periodic monitoring of anticonvulsant levels should be conducted.

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

Ribavirin

No clinically significant medicines interactions have been observed between the tenofovir disoproxil fumarate in TRENVIR and ribavirin. Following multiple dosing to HIV-negative subjects receiving single doses of ribavirin, steady state tenofovir pharmacokinetics were similar to those

observed in previous studies, indicating lack of clinically significant medicine interactions between ribavirin and the tenofovir in TRENVIR.

Rifamycin

Rifampicin reduced efavirenz AUC by 26 % and C_{max} by 20 % in 12 uninfected volunteers. The dose of efavirenz must be increased to 800 mg/day when taken with rifampicin. Therefore, if TRENVIR is co-administered with rifampicin, an additional 200 mg/day of efavirenz is recommended. No dose adjustment of rifampicin is recommended when given with TRENVIR.

Co-administration of single doses of rifabutin 300 mg and efavirenz 600 mg resulted in decreases of 38 % (90 % CI -28 % to -36 %) in AUC, 32 % (-15 % to -46 %) in C_{max} and 45 % (-31 % to - 56 %) in C_{min} of rifabutin. The AUC and C_{max} of efavirenz remained unchanged, while the C_{min} decreased with 12 % (-24 % to -1 %). The daily dose of rifabutin should be increased by 50 % when given with TRENVIR. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 to 3 times a week in combination with TRENVIR.

Ritonavir

When efavirenz was given with ritonavir 500 mg or 600 mg twice daily, the combination was not well tolerated (e.g., dizziness, nausea, paraesthesia, and elevated liver enzymes occurred.) Efavirenz AUC, C_{max} and C_{min} increased with 21 % (+10 % to +34 %), 14 % (+4 % to +26 %), and 25 % (+7 % to +46 %), respectively. Sufficient data on the tolerability of efavirenz with low-dose ritonavir (100 mg, once or twice daily) are not available. Co-administration of ritonavir at doses of 600 mg and TRENVIR is not recommended. When using TRENVIR in a regimen including low-dose ritonavir, the possibility of an increase in the incidence of efavirenz-associated adverse events should be considered, due to possible pharmacodynamic interaction.

Saquinavir

When saquinavir (1200 mg given 3 times a day, soft capsule formulation) was given with efavirenz, the saquinavir AUC and C_{max} were decreased by 62 % and 50 %, respectively, while the efavirenz AUC, C_{max} and C_{min} were decreased by 12 %, 13 % and 14 %, respectively. Use of TRENVIR in combination with saquinavir as the sole protease inhibitor is not recommended.

No data are available on the potential interactions of efavirenz with the combination of saquinavir and ritonavir. Insufficient data are available to make a dosing recommendation for saquinavir/ritonavir when dosed with TRENVIR. Co-administration of saquinavir/ritonavir and TRENVIR is not recommended.

Selective serotonin reuptake inhibitors (SSRI)

When co-administered with TRENVIR, sertraline dose increases should be guided by clinical response, since co-administration of sertraline 50 mg with efavirenz 600 mg resulted in mean decreases in the sertraline AUC, C_{max} and C_{min} of 39 %, 29 % and 46 %, respectively.

TRENVIR and paroxetine can be co-administered without dose adjustment. Co-administration of efavirenz and paroxetine did not result in any changes in the AUC, C_{max} or C_{min} of either paroxetine or efavirenz.

TRENVIR and fluoxetine can be co-administered without dose adjustment, since fluoxetine shares a similar metabolic profile with paroxetine, i.e., strong CYP2D6 inhibitory effect. A similar lack of interaction would therefore be expected with fluoxetine.

Stavudine

No clinically significant medicine interactions have been observed between the emtricitabine in TRENVIR and stavudine. Co-administration of single doses of stavudine 40 mg with a single dose of emtricitabine 200 mg did not alter the C_{max} or AUC of emtricitabine or stavudine.

St. John's wort (Hypericum perforatum)

Patients on TRENVIR should not concomitantly use products containing St. John's wort (*Hypericum perforatum*), since it may be expected to result in reduced plasma concentrations of efavirenz. This effect is due to an induction of CYP3A4 and may result in loss of therapeutic effect and development of resistance.

Voriconazole

Co-administration of standard doses of efavirenz and voriconazole is contra-indicated due to significant increases in the AUC and C_{max} of efavirenz and significant decreases in the AUC and C_{max} of voriconazole. Since TRENVIR is a fixed-dose combination product, the dose of efavirenz cannot be altered; therefore, voriconazole and TRENVIR must not be co-administered (see **section 4.3** and **4.4**).

Other important medicine interaction information for TRENVIR is summarized in **Table 2** and **Table 3**. The medicine interactions described are based on studies conducted with efavirenz, emtricitabine or tenofovir DF as individual medicines or are potential medicine interactions, no medicine interaction studies have been conducted using TRENVIR. The tables include potentially significant interactions but are not all inclusive.

Table 2: Medicines that are contraindicated or not recommended for use with TRENVIR

Medicine class: Medicine name	**Clinical comment**

Antifungal: Voriconazole	Contraindicated because efavirenz significantly decreases voriconazole plasma concentrations and co-administration may decrease the therapeutic effectiveness of voriconazole. Also, voriconazole significantly increases efavirenz plasma concentrations, which may increase the risk of efavirenz associated side effects.
Antihistamine: Astemizole, terfenadine	Contraindicated due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.
Anti-migraine: Ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine)	Contraindicated due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterised by peripheral vasospasm and ischaemia of the extremities and other tissue.
Antiretrovirals: Efavirenz, emtricitabine, tenofovir DF, lamivudine	Not for use with TRENVIR because the active ingredients – emtricitabine, tenofovir DF, emtricitabine/tenofovir DF and efavirenz are components of TRENVIR. Lamivudine is similar to emtricitabine.
Benzodiazepines: Midazolam, triazolam	Contraindicated due to potential for serious and/or life-threatening reactions such as prolonged increased sedation of respiratory depression.
Calcium channel blocker: Bepridil	Contraindicated due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.
Nephrotoxic medicinal product. Some examples include, but are not limited to, aminoglycosides,	Use of TRENVIR should be avoided with concurrent or recent use of a nephrotoxic medicinal product (see **section 4.4**).

amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2	
QT Prolonging Drugs that could lead to Torsade de Pointes: Antiarrhythmics of classes IA and III, Neuroleptics and antidepressant agents, certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole, and triazole antifungal agents, certain non-sedating antihistaminics: (terfenadine, astemizole), cisapride, flecainide, certain antimalarials and methadone (see **section 4.3**)	TRENVIR is contraindicated with concomitant use of medicines that are known to prolong the QTc interval.
GI motility medicine: Cisapride	Contraindicated due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.
Neuroleptic: Pimozide	Contraindicated due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.
Atazanavir/ritonavir	Not recommended; Insufficient data are available to make a dosing recommendation for atazanavir/ritonavir in combination with efavirenz/emtricitabine/tenofovir disoproxil

Didanosine	Not recommended (see **section 4.4**)
Sofosbuvir/velpatasvir and sofosbuvir/velpatasvir/voxilaprevir	Not recommended (see **section 4.4**)
Renally eliminated medicinal products	Since emtricitabine and tenofovir are primarily eliminated by the kidneys, co-administration of TRENVIR 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
St. John's wort *(Hypericum perforatum)*	Not recommended: Expected to substantially decrease plasma levels of efavirenz 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**). It has not been studied in combination with efavirenz.
Hepatitis C antivirals: Elbasvir / Grazoprevir + Efavirenz	Co-administration of TRENVIR with elbasvir/grazoprevir is contraindicated because it may lead to loss of virologic response to elbasvir/grazoprevir. This loss is due to significant decreases in elbasvir/grazoprevir plasma concentrations caused by CYP3A4 or P-gp induction

Ledipasvir/Sofosbuvir	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see **section 4.4**)

Table 3: Established and other potentially significant medicine interactions: Alternation in dose or regimen may be recommended based on medicine interaction studies or predicted interactions

Concomitant medicine class: Medicine name	**Effect**	**Clinical comment**
Antiretroviral medicines		
Protease inhibitor: Amprenavir	↓ Amprenavir concentration	Efavirenz has the potential to decrease serum concentrations of amprenavir.
Protease inhibitor: Fosamprenavir calcium	↓ Amprenavir concentration	Fosamprenavir (unboosted): appropriate doses of fosamprenavir and TRENVIR with respect to safety and efficacy have not been established. Fosamprenavir/ritonavir: An additional 100 mg/day (300 mg total) of ritonavir is recommended when TRENVIR is administered with fosamprenavir/ ritonavir once daily. No change in the ritonavir

		dose is required when TRENVIR is administered with fosamprenavir plus ritonavir twice daily.
Protease inhibitor: Atazanavir	↓ Atazanavir concentration ↑ Tenofovir concentration	Plasma concentrations of atazanavir were decreased by both efavirenz and tenofovir DF. Sufficient data are not available to make a dosing recommendation for atazanavir or atazanavir/ ritonavir with TRENVIR. Therefore, co-administration of TRENVIR and atazanavir is not recommended due to concerns regarding decreased atazanavir concentrations.
Protease inhibitor: Indinavir	↓ Indinavir concentration	The optimal dose of indinavir, when given in combination with efavirenz, is not known. Increasing the indinavir dose to 1 000 mg every 8 hours does not compensate for the increased indinavir metabolism due to efavirenz.

Protease inhibitor: Lopinavir/ritonavir	↓ Lopinavir concentration ↑ Tenofovir concentration	A dose increase of lopinavir/ritonavir to 600/150 mg (3 tablets) twice daily may be considered when used in combination with efavirenz in treatment-experienced patients where decreased susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). Patients should be monitored for tenofovir associated adverse events. TRRENVIR should be discontinued in patients who develop tenofovir-associated adverse events.
Protease inhibitor: Ritonavir	↑ Ritonavir concentration ↑ Efavirenz concentration	When ritonavir 500 mg every 12 hours was co-administered with efavirenz 600 mg once daily, the combination was associated with a higher frequency of adverse clinical experiences (e.g. dizziness, nausea, paraesthesia) and laboratory abnormalities (elevated liver enzymes). Monitoring of liver enzymes is

		recommended when TRENVIR is used in combination with ritonavir.
Protease inhibitor: Saquinavir	↓ Saquinavir concentration	Should not be used as sole protease inhibitor in combination with TRENVIR.
Protease inhibitor: Atazanavir/ritonavir/ tenofovir disoproxil (300 mg q.d./100 mg q.d./245 mg q.d.)	Atazanavir concentration and exposure C_{max}: ↓ 28% (↓ 50 to ↑ 5) C_{min}: ↓ 26% (↓ 46 to ↑ 10) AUC: ↓ 25% (↓ 42 to ↓ 3) Co-administration of atazanavir/ritonavir with tenofovir resulted in increased exposure totenofovir. Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders	Co-administration of atazanavir/ritonavir and TRENVIR is not recommended.
Protease inhibitor: Atazanavir/ritonavir/	↔ in Atazanavir (pm) exposure and ↑ in peak	

efavirenz (400 mg q.d./100 mg q.d./600 mg q.d., all administered with food) Atazanavir/ritonavir/ efavirenz (400 mg q.d./200 mg q.d./600 mg q.d., all administered with food)	concentrations (C_{max}) and in trough concentrations (C_{min}) C_{max}: ↑ 17%* (↑ 8 to ↑ 27) C_{min}: ↓ 42%* (↓ 31 to ↓ 51) AUC: ↔* (↓ 9% to ↑ 10%) ↔ in Atazanavir (pm) exposure and ↔ in peak concentrations (C_{max}) and ↑ in trough concentrations (C_{min}) C_{max}: ↔*/** (↓ 5% to ↑ 26%) C_{min}: ↑ 12%*/** (↓ 16 to ↑ 49) AUC: ↔*/** (↓ 10% to ↑ 26%) (CYP3A4 induction). * When compared to atazanavir 300 mg / ritonavir 100 mg q.d. in the evening without	

	efavirenz. This decrease in atazanavir Cmin might negatively impact the efficacy of atazanavir. ** based on historical comparison. Co-administration of efavirenz with atazanavir/ritonavir is not recommended.	
Protease inhibitor: Atazanavir/ritonavir/ emtricitabine	Interaction not studied.	
Protease inhibitor: 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 peak concentration (C_{max}), trough concentration (C_{min}) and exposure (AUC) C_{min}: ↓ 31% C_{max}: ↓ 15% AUC: ↓ 13% (CYP3A4 induction) ↑ Efavirenz peak concentration (C_{max}),	TRENVIR in combination with darunavir / ritonavir 800/100 mg once daily may result in suboptimal darunavir $C_{min.}$ If TRENVIR 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

	trough concentration (C_{min}), and exposure (AUC) C_{min}: ↑ 17% C_{max}: ↑ 15% AUC: ↑ 21% (CYP3A4 inhibition)	with TRENVIR. 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.
Protease inhibitor: Darunavir/ritonavir/tenofovir disoproxil (300 mg b.i.d.*/100 mg b.i.d./245 mg q.d.) *lower than recommended dose	↔ in Darunavir trough concentrations (C_{min}) and exposure (AUC) ↑Tenofovir trough concentrations (C_{min}) and exposure C_{min}: ↑ 37% AUC: ↑ 22%	
Protease inhibitor: Darunavir/ritonavir/emtricitabine	Interaction not studied. Based on the different elimination pathways, no interaction is expected.	
Protease inhibitor: Fosamprenavir/ritonavir/efavirenz (700 mg b.i.d./100 mg b.i.d./600 mg q.d.)	No clinically significant pharmacokinetic interaction.	TRENVIR and fosamprenavir / ritonavir can be co-administered without dose adjustment. See ritonavir row below
Protease inhibitor:	Interaction not studied.	

Fosamprenavir/ritonavir/emtricitabine		
Protease inhibitor: Fosamprenavir/ritonavir/tenofovir disoproxil	Interaction not studied.	
Protease inhibitor: Indinavir/efavirenz (800 mg q8h/200 mg q.d.)	↔ in Efavirenz peak concentration (C_{max}) and trough concentrations (C_{min}) and exposure (AUC) ↓ Indinavir trough concentrations (C_{min}) and exposure: C_{min}: ↓ 40% AUC: ↓ 31% (↓ 8 to ↓ 47) A similar reduction in indinavir exposures was observed when indinavir 1,000 mg q8h was given with efavirenz 600 mg q.d. (CYP3A4 induction) For co-administration of efavirenz with low-dose ritonavir in combination	Insufficient data are available to make a dosing recommendation for indinavir when dosed with TRENVIR. 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 TRENVIR and indinavir.

	with a protease inhibitor, see section on ritonavir below.	
Protease inhibitor: Indinavir/emtricitabine (800 mg q8h/200 mg q.d.)	↔ in Indinavir peak concentrations (C_{max}) and exposure (AUC) ↔ in Emtricitabine peak concentrations (C_{max}) and exposure (AUC)	
Protease inhibitor: Indinavir/tenofovir disoproxil (800 mg q8h/245 mg q.d.)	↔ in Indinavir peak concentrations (C_{max}) and exposure (AUC) and ↔ in Tenofovir peak concentrations (C_{max}) and exposure (AUC)	
Protease inhibitor: Lopinavir/ritonavir/tenofovir disoproxil (400 mg b.i.d./100 mg b.i.d./245 mg q.d.)	↔ in Lopinavir/Ritonavir peak concentrations (C_{max}), ↑ trough concentrations (C_{min}), and exposure (AUC) ↔ in Tenofovir peak concentrations (C_{max}) and trough	Insufficient data are available to make a dosing recommendation for lopinavir /ritonavir when dosed with TRENVIR. Co-administration of lopinavir/ritonavir and TRENVIR is not recommended.

	concentrations (C_{min}), and exposure (AUC) C_{min}: ↑ 51% (↑ 37 to ↑ 66) AUC: ↑ 32% (↑ 25 to ↑ 38) Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders.	
Protease inhibitor: 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	

	tolopinavir/ritonavir (soft capsules)	
Protease inhibitor: Lopinavir/ritonavir tablets /efavirenz (400/100 mg b.i.d./600 mg q.d.) (500/125 mg b.i.d./600 mg q.d.)	400/100 mg twice daily without efavirenz (historical data). Lopinavir concentrations: ↓ 30-40% Lopinavir concentrations: similar to lopinavir/ritonavir 400/100 mg twice daily without efavirenz. Dosage adjustment of lopinavir/ritonavir is necessary when given with efavirenz. For co-administration of efavirenz with low-dose ritonavir in combination with a protease inhibitor, see section on ritonavir below.	
Protease inhibitor:	Interaction not studied.	

Lopinavir/ritonavir/emtricitabine		
Protease inhibitor: Ritonavir/efavirenz (500 mg b.i.d./600 mg q.d.)	Morning: ↑ Ritonavir peak concentrations (C_{max}), trough concentration (C_{min}), and exposure (AUC) Morning C_{max}: ↑ 24% (↑ 12 to ↑38) Morning C_{min}: ↑ 42% (↑ 9 to ↑ 86) Morning AUC: ↑ 18% (↑ 6 to ↑ 33) Evening: ↔ in Ritonavir evening peak concentrations (C_{max}) and exposure (AUC), and ↑ in trough concentrations (C_{min}) Evening C_{min}: ↑ 24% (↑ 3 to ↑ 50) ↑ Efavirenz peak concentrations (C_{max}), trough concentration	Co-administration of ritonavir at doses of 600 mg and TRENVIR is not recommended. When using TRENVIR 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.

	(C_{min}), and exposure (AUC) C_{max}: ↑ 14% (↑ 4 to ↑ 26) C_{min}: ↑ 25% (↑ 7 to ↑ 46) AUC: ↑ 21% (↑ 10 to ↑ 34) (inhibition of CYP-mediated oxidative metabolism) When efavirenz was given with ritonavir 500 mg or 600 mg twice daily, the combination was not well tolerated (for example, dizziness, nausea, paraesthesia and elevated liver enzymes occurred). Sufficient data on the tolerability of efavirenz with low-dose ritonavir (100 mg, once or twice daily) are not available.	
Protease inhibitor: ritonavir/emtricitabine	Interaction not studied.	

Protease inhibitor: Ritonavir/tenofovir disoproxil	Interaction not studied.	
Protease inhibitor: 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 TRENVIR. Co-administration of saquinavir/ritonavir and TRENVIR is not recommended. Use of TRENVIR in combination with saquinavir as the sole protease inhibitors not recommended.
Protease inhibitor: Saquinavir/ritonavir/tenofovir disoproxil	There were no clinically significant pharmacokinetic interactions when tenofovir disoproxil was co-administered with ritonavir boosted saquinavir.	
Protease inhibitor: Saquinavir/ritonavir/tenofovir disoproxil	Interaction not studied.	
NRTIs and NNRTIs: Didanosine	↑ Didanosine concentration	Higher didanosine concentrations could potentiate didanosine associated adverse events, including pancreatitis and

		neuropathy. In adults weighing more than 60 kg, the didanosine dose should be reduced to 250 mg if co-administered with TRENVIR. Data is not available to recommend a dose adjustment of didanosine for patients weighing less than 60 kg. When co-administered, TRENVIR and didanosine may be taken under fasted conditions or with a light meal (less than 400 kcal, 20 % fat). Co-administration of didanosine buffered formulation with TRENVIR should be under fasted conditions. Co-administration of TRENVIR and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse events. For additional information, please consult the didanosine professional information.

NRTIs and NNRTIs: Didanosine/tenofovir disoproxil	Co-administration of tenofovir disoproxil and didanosine results in a 40-60% increase in systemic exposure to didanosine.	Co-administration of TRENVIR and didanosine is not recommended (see **section 4.4**). Increased systemic exposure to didanosine may increase didanosine related adverse reactions. Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported. Co-administration of tenofovir disoproxil and didanosine at a dose of 400 mg daily has been associated with a significant decrease in CD4 cell count, possibly due to an intracellular interaction increasing phosphorylated (i.e. active) didanosine. A decreased dosage of 250 mg didanosine co-administered with tenofovir disoproxil therapy has been associated with reports of high rates of virological failure within several tested combinations for the treatment of HIV-1 infection.
Didanosine/Efavirenz	Interaction not studied.	
Didanosine/Emtricitabine	Interaction not studied.	

NRTIs and NNRTIs: NRTIs/efavirenz	Specific interaction studies have not been performed with efavirenz and NRTIs other than lamivudine, zidovudine and tenofovir disoproxil. Clinically significant interactions have not been found and would not be expected since the NRTIs are metabolised via a different route than efavirenz and would be unlikely to compete for the same metabolic enzymes and elimination pathways.	Due to the similarity between lamivudine and emtricitabine, a component of TRENVIR, should not be administered concomitantly with lamivudine (see **section 4.4**).
NRTIs and NNRTIs: NNRTIs/efavirenz	Interaction not studied.	Since use of two NNRTIs proved not beneficial in terms of efficacy and safety, co-administration of TRENVIR and another NNRTI is not recommended.

Integrase strand transfer inhibitor: Raltegravir/efavirenz (400 mg single dose)	↓ Raltegravir peak concentrations (C_{max}), concentration at 12 h (C_{12h}), and exposure (AUC) C_{12h}: ↓ 21% C_{max}: ↓ 36% AUC: ↓ 36% (UGT1A1 induction)	TRENVIR and raltegravir can be co-administered without dose adjustment.
Integrase strand transfer inhibitor: Raltegravir/tenofovir disoproxil (400 mg b.i.d.)	↑ Raltegravir peak concentrations (C_{max}), concentration at 12 h (C_{12h}), and exposure (AUC) C_{max}: ↑ 64% C_{12h}: ↑ 3% AUC: ↑ 49% (mechanism of interaction unknown) ↓ Tenofovir peak concentrations (C_{max}), concentration at 12 h (C_{12h}), and exposure (AUC) C_{max}: ↓ 23%	

	C_{12h}: ↓ 13% AUC: ↓ 10%	
Integrase strand transfer inhibitor: Raltegravir/emtricitabine	Interaction not studied.	
CCR5 antagonist: Maraviroc/efavirenz (100 mg b.i.d./600 mg q.d.)	↓ Maraviroc peak concentrations (C_{max}), exposure at 12 h (AUC_{12h}) C_{max}: ↓ 51% (↓ 37 to ↓ 62) AUC_{12h}: ↓ 45% (↓ 38 to ↓ 51) Efavirenz concentrations not measured, no effect is expected.	Refer to the Summary of Product Characteristics for the medicinal product containing maraviroc.
CCR5 antagonist: Maraviroc/ tenofovir disoproxil (300 mg b.i.d./245 mg q.d.)	↔ in Maraviroc peak concentrations (C_{max}), exposure at 12 h (AUC_{12h}) Tenofovir concentrations not measured, no effect is expected.	

CCR5 antagonist: Maraviroc/ emtricitabine	Interaction not studied.	
Other medicines		
Anticoagulant: Warfarin	↑ Or ↓ warfarin concentration	Plasma concentrations and effects (INR) potentially increased or decreased by efavirenz.
Anticoagulant: 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 TRENVIR.
Anticonvulsants: Carbamazepine	↓ Carbamazepine concentration ↓ Efavirenz concentration	There are insufficient data to make a dose recommendation for TRENVIR. Alternative anticonvulsant treatment should be used.
Anticonvulsants: Phenytoin, Phenobarbital	↓ Anti-convulsant concentration ↓ Efavirenz concentration	Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.

Anticonvulsants: Carbamazepine/efavirenz (400 mg q.d./600 mg q.d.)	↓ Carbamazepine peak concentration (C_{max}), trough concentration (C_{min}), and exposure (AUC) C_{max}: ↓ 20% (↓ 15 to ↓ 24) C_{min}: ↓ 35% (↓ 24 to ↓ 44) AUC: ↓ 27% (↓ 20 to ↓ 33) (CYP3A4 induction) ↓ Efavirenz peak concentration (C_{max}), trough concentration (C_{min}), and exposure (AUC) AUC: ↓ 36% (↓ 32 to ↓ 40) C_{max}: ↓ 21% (↓ 15 to ↓ 26) C_{min}: ↓ 47% (↓ 41 to ↓ 53) (CYP2B6 induction) Co-administration of higher doses of either efavirenz or	No dose recommendation can be made for the use of TRENVIR with carbamazepine. An alternative anticonvulsant should be considered. Carbamazepine plasma levels should be monitored periodically.

	carbamazepine has not been studied.	
Anticonvulsants: Carbamazepine/emtricitabine	Interaction not studied.	
Anticonvulsants: Carbamazepine/tenofovir disoproxil	Interaction not studied.	
Anticonvulsants: Phenytoin, phenobarbital, and other anticonvulsants that are substrates of CYP isozymes	Interaction not studied with TRENVIR. There is a potential for reduction or increase in the plasma concentrations of phenytoin, phenobarbital and other anticonvulsants that are substrates of CYP isozymes with efavirenz.	When TRENVIR is co-administered with an anticonvulsant that is a substrate of CYP isozymes, periodic monitoring of anticonvulsant levels should be conducted.
Anticonvulsants: 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.	TRENVIR and valproic acid can be co-administered without dose adjustment. Patients should be monitored for seizure control.

Anticonvulsants: Valproic acid/emtricitabine	Interaction not studied.	
Anticonvulsants: Valproic acid/tenofovir disoproxil	Interaction not studied.	
Anticonvulsants: 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.	TRENVIR and vigabatrin or gabapentin can be co-administered without dose adjustment.
Anticonvulsants: Vigabatrin/emtricitabine Gabapentin/emtricitabine	Interaction not studied.	
Anticonvulsants: Vigabatrin/tenofovir disoproxil Gabapentin/tenofovir disoproxil	Interaction not studied.	

Antidepressant: Sertraline	↓ Sertraline concentration	Increases in sertraline dose should be guided by clinical response.
Antidepressant: Sertraline/efavirenz (50 mg q.d./600 mg q.d.)	↓ Sertraline peak concentration (C_{max}), trough concentration (C_{min}), and exposure (AUC) AUC: ↓ 39% (↓ 27 to ↓ 50) C_{max}: ↓ 29% (↓ 15 to ↓ 40) C_{min}: ↓ 46% (↓ 31 to ↓ 58) ↔ in Efavirenz trough concentration (C_{min}) and exposure (AUC) and ↑ peak concentration (C_{max}) C_{max}: ↑ 11% (↑ 6 to ↑ 16) (CYP3A4 induction)	When co-administered with TRENVIR, sertraline dose increases should be guided by clinical response.
Antidepressant: Sertraline/ emtricitabine	Interaction not studied.	
Antidepressant: Sertraline/tenofovir disoproxil	Interaction not studied.	

Antidepressant: Paroxetine/efavirenz (20 mg q.d./600 mg q.d.)	↔ in Paroxetine peak concentration (C_{max}), trough concentration (C_{min}), and exposure (AUC) ↔ in Efavirenz peak concentration (C_{max}), trough concentration (C_{min}), and exposure (AUC)	TRENVIR and paroxetine can be co-administered without dose adjustment.
Antidepressant: Paroxetine/emtricitabine	Interaction not studied.	
Antidepressant: Paroxetine/tenofovir disoproxil	Interaction not studied.	
Antidepressant: 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.	TRENVIR and fluoxetine can be co-administered without dose adjustment.
Antidepressant: Fluoxetine/emtricitabine	Interaction not studied.	
Antidepressant:	Interaction not studied.	

Fluoxetine/tenofovir disoproxil		
Hepatitis C antivirals: Elbasvir/grazoprevir + efavirenz	↓ Elbasvir peak concentration (C_{max}) and exposure (AUC) C_{max}: ↓ 45% AUC: ↓ 54% (CYP3A4 or P-gp induction -effect on elbasvir) ↓ Grazoprevir peak concentration (C_{max}) and exposure (AUC) C_{max}: ↓ 87% AUC: ↓ 83% (CYP3A4 or P-gp induction -effect on grazoprevir) ↔ in Efavirenz peak concentration (C_{max}) and exposure (AUC)	Co-administration of TRENVIR with elbasvir/grazoprevir is contraindicated because it may lead to loss of virologic response to elbasvir/grazoprevir. This loss is due to significant decreases in elbasvir/grazoprevir plasma concentrations caused by CYP3A4 or P-gp induction. Refer to the Summary of Product Characteristics for elbasvir/grazoprevir for more information.
Hepatitis C antivirals: Glecaprevir/pibrentasvir/efavirenz	Expected*:* ↓ Glecaprevir concentration ↓ Pibrentasvir concentration	Concomitant administration of glecaprevir/pibrentasvir with efavirenz,a component of TRENVIR, may significantly decrease plasma concentrations

		of glecaprevir and pibrentasvir, leading to reduced therapeutic effect. Co-administration of glecaprevir/pibrentasvir with TRENVIR is not recommended. Refer to the prescribing information for glecaprevir/pibrentasvir for more information.
Hepatitis C antivirals: Ledipasvir/sofosbuvir (90 mg/400 mg q.d.) + Efavirenz/emtricitabine/tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)	↓ in Ledipasvir peak concentration (C_{max}), trough concentration (C_{min}), and exposure (AUC) C_{max}: ↓ 34% (↓ 41 to ↑ 25) C_{min}: ↓ 34% (↓ 43 to ↑ 24) AUC: ↓ 34% (↓ 41 to ↓ 25) ↔ in Sofosbuvir peak concentration (C_{max}) and exposure (AUC) ↔ in GS-3310071 peak concentration (C_{max}), trough	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see **section 4.4**).

	concentration (C_{min}), and exposure (AUC) ↔ in Efavirenz peak concentration (C_{max}), trough concentration (C_{min}), and exposure (AUC) ↔ in Emtricitabine peak concentration (C_{max}), trough concentration (C_{min}), and exposure (AUC) ↑ Tenofovir peak concentration (C_{max}), trough concentration (C_{min}), and exposure (AUC) AUC: ↑ 98% (↑ 77 to ↑ 123) C_{max}: ↑ 79% (↑ 56 to ↑ 104) C_{min}: ↑ 163% (↑ 137 to ↑ 197)	

Hepatitis C antivirals: Sofosbuvir/velpatasvir (400 mg/100 mg q.d.) + Efavirenz/emtricitabine/tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)	↑ Sofosbuvir peak concentration (C_{max}) and ↔ in exposure (AUC) C_{max}: ↑ 38% (↑ 14 to ↑ 67) ↔ in GS-3310071 peak concentration (C_{max}), trough concentration (C_{min}), and exposure (AUC) ↓ Velpatasvir peak concentration (C_{max}), trough concentration (C_{min}), and exposure (AUC) C_{max}: ↓ 47% (↓ 57 to ↓ 36) C_{min}: ↓ 57% (↓ 64 to ↓ 48) AUC: ↓ 53% (↓ 61 to ↓ 43) ↔ in Efavirenz peak concentration (C_{max}), trough concentration (C_{min}), and exposure (AUC)	Concomitant administration of TRENVIR and sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir is expected to decrease plasma concentrations of velpatasvir and voxilaprevir. Co- administration of TRENVIR with sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir is not recommended (see **section 4.4**).

	↔ in Emtricitabine peak concentration (C_{max}), trough concentration (C_{min}), and exposure (AUC) ↑ Tenofovir peak concentration (C_{max}), trough concentration (C_{min}), and exposure (AUC) C_{max}: ↑ 77% (↑ 53 to ↑ 104) C_{min}: ↑ 121% (↑ 100 to ↑ 143) AUC: ↑ 81% (↑ 68 to ↑ 94)	
Hepatitis C antivirals: Sofosbuvir/velpatasvir/voxilaprevir (400 mg/100 mg/100 mg q.d.) + Efavirenz/emtricitabine/tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)	Interaction only studied with sofosbuvir/velpatasvir. Expected: ↓ Voxilaprevir concentration	

Hepatitis C antivirals Sofosbuvir (400 mg q.d.) + Efavirenz/Emtricitabine/Tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)	↓ Sofosbuvir peak concentration (C_{max}) C_{max}: ↓ 19% (↓ 40 to ↑ 10) ↓ GS-3310071 peak concentration (C_{max}) and ↔ in exposure (AUC) C_{max}: ↓ 23% (↓ 30 to ↑ 16) ↔ in Efavirenz peak concentration (C_{max}), trough concentration (C_{min}), and exposure (AUC) ↔ in Emtricitabine peak concentration (C_{max}), trough concentration (C_{min}), and exposure (AUC) ↑ Tenofovir peak concentration (C_{max}), and ↔ in trough concentration (C_{min}), and exposure (AUC) C_{max}: ↑ 25% (↑ 8 to ↑ 45)	TRENVIR and sofosbuvir can be co-administered without dose adjustment.

Antibiotics: Clarithromycin/efavirenz (500 mg b.i.d./400 mg q.d.)	↓ Clarithromycin peak concentration (C_{max}) and exposure (AUC) C_{max}: ↓ 26 % (↓ 15 to ↓ 35) AUC: ↓ 39 % (↓ 30 to ↓ 46) ↑ Clarithromycin 14-hydroxymetabolite peak concentration (C_{max}) and exposure (AUC) C_{max}: ↑ 49% (↑ 32 to ↑ 69) AUC: ↑ 34% (↑ 18 to ↑ 53) ↑ Efavirenz peak concentration (C_{max}) and ↔ in exposure (AUC) C_{max}: ↑ 11% (↑ 3 to ↑ 19) (CYP3A4 induction) Rash developed in 46% of uninfected volunteers receiving efavirenz and clarithromycin.	The clinical significance of these changes in clarithromycin plasma levels is not known. Alternatives to clarithromycin (e.g. azithromycin) may be considered. Other macrolide antibiotics, such as erythromycin, have not been studied in combination with TRENVIR.

Antibiotics Clarithromycin/emtricitabine	Interaction not studied.	
Antibiotics Clarithromycin/tenofovir disoproxil	Interaction not studied.	
Antifungals: Itraconazole Ketoconazole	↓ Itraconazole concentration ↓ Hydroxy itraconazole concentration ↓ Ketoconazole concentration	Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered. Medicine interaction studies with TRENVIR and ketoconazole have not been conducted. Efavirenz has the potential to decrease plasma concentrations of ketoconazole.
Antifungals: Itraconazole/Efavirenz (200 mg b.i.d./600 mg q.d.)	↓ Itraconazole peak concentration (C_{max}), trough concentration (C_{min}), and exposure (AUC) C_{max}: ↓ 37% (↓ 20 to ↓ 51) C_{min}: ↓ 44% (↓ 27 to ↓ 58) AUC: ↓ 39% (↓ 21 to ↓ 53)	Since no dose recommendation can be made for itraconazole when used with TRENVIR, an alternative antifungal treatment should be considered.

	(CYP3A4induction) ↓ Hydroxyitraconazole peak concentration (C_{max}), trough concentration (C_{min}), and exposure (AUC) AUC: ↓ 37% (↓ 14 to ↓ 55) C_{max}: ↓ 35% (↓ 12 to ↓ 52) C_{min}: ↓ 43% (↓ 18 to ↓ 60) ↔ in Efavirenz peak concentration (C_{max}), trough concentration (C_{min}), and exposure (AUC)	
Antifungals: Itraconazole/emtricitabine	Interaction not studied.	
Antifungals: Itraconazole/tenofovir disoproxil	Interaction not studied.	
Antifungals: Posaconazole/efavirenz (-/400 mg q.d.)	↓ Posaconazole peak concentration (C_{max}) and exposure (AUC) C_{max}: ↓ 45%	Concomitant use of posaconazole and TRENVIR should be avoided unless the

	AUC: ↓ 50% (UDP-G induction)	benefit to the patient outweighs the risk.
Antifungals: Posaconazole/emtricitabine	Interaction not studied.	
Antifungals: Posaconazole/tenofovir disoproxil	Interaction not studied.	
Antifungals: Voriconazole/Efavirenz (200 mg b.i.d./400 mg q.d.)	↓ Voriconazole peak concentration (C_{max}) and exposure (AUC) C_{max}: ↓ 61% AUC: ↓ 77% ↑ Efavirenz peak concentration (C_{max}) and exposure (AUC) C_{max}: ↑ 38% AUC: ↑ 44% (competitive inhibition of oxidative metabolism) Co-administration of standard doses of efavirenz and voriconazole is contraindicated (see **section 4.3**).	Since TRENVIR is a fixed-dose combination product, the dose of efavirenz cannot be altered; therefore, voriconazole and TRENVIR must not be co-administered.

Antifungals: Voriconazole/emtricitabine	Interaction not studied.	
Antifungals: Voriconazole/tenofovir disoproxil	Interaction not studied.	
Anti-infective: Clarithromycin	↓ Clarithromycin concentration ↑ 14–OH metabolite concentration	Clinical significance unknown. In uninfected volunteers, 46 % developed rash while receiving efavirenz and clarithromycin. No dose adjustment of TRENVIR is recommended when given with clarithromycin. Alternatives to clarithromycin, such as azithromycin should be considered. Other macrolide antibiotics, such as erythromycin, have not been studied in combination with TRENVIR.
Antimycobacterial: Rifabutin	↓ Rifabutin concentration	Increase daily dose of rifabutin by 50%. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week.

Antimycobacterial: Rifampicin	↓ Efavirenz concentration	Clinical significance of reduced efavirenz concentration is unknown. Dosing recommendations for concomitant use of TRENVIR and rifampicin have not been established.
Antimycobacterial: Rifabutin/efavirenz (300 mg q.d./600 mg q.d.)	↓ Rifabutin peak concentration (C_{max}), trough concentration (C_{min}), and exposure (AUC) C_{max}: ↓ 32% (↓ 15 to ↓ 46) C_{min}: ↓ 45% (↓ 31 to ↓ 56) AUC: ↓ 38% (↓ 28 to ↓ 47) ↔ in Efavirenz peak concentration (C_{max}) and exposure (AUC), and ↓ in trough concentration (C_{min}) C_{min}: ↓ 12% (↓ 24 to ↑ 1) (CYP3A4 induction)	The daily dose of rifabutin should be increased by 50% when given with TRENVIR. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week in combination with TRENVIR. 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**).

Antimycobacterial: Rifabutin/emtricitabine	Interaction not studied.	
Antimycobacterial: Rifabutin/tenofovir disoproxil	Interaction not studied.	
Antimycobacterial: Rifampicin/efavirenz (600 mg q.d./600 mg q.d.)	↓ Efavirenz peak concentration (C_{max}), trough concentration (C_{min}), and exposure (AUC) C_{max}: ↓ 20% (↓ 11 to ↓ 28) C_{min}: ↓ 32% (↓ 15 to ↓ 46) AUC: ↓ 26% (↓ 15 to ↓ 36) (CYP3A4 and CYP2B6 induction)	When TRENVIR is taken with rifampicin in patients weighing 50 kg or greater, an additional 200 mg/day (800 mg total) of efavirenz may provide exposure similar to a daily efavirenz dose of 600 mg when taken without rifampicin. The clinical effect of this dose adjustment has not been adequately evaluated. Individual tolerability and virological response should be considered when making the dose adjustment (see **section 5.2**). No dose adjustment of rifampicin is recommended when given with TRENVIR.
Antimycobacterial: Rifampicin/tenofovir disoproxil (600 mg q.d./245 mg q.d.)	↔ in Rifampicin peak concentration (C_{max}) and exposure (AUC) ↔ in Tenofovir peak concentration (C_{max}) and exposure (AUC)	
Antimycobacterial: Rifampicin/emtricitabine	Interaction not studied.	

Antimalarials: Artemether/lumefantrine/efavirenz (20/120 mg tablet, 6 doses of 4 tablet search over 3 days/600 mg q.d.)	↓ Artemether peak concentration (C_{max}) and exposure (AUC) C_{max}: ↓ 21% AUC: ↓ 51% ↓ Dihydroartemisinin (active metabolite) peak concentration (C_{max}) and exposure (AUC) C_{max}: ↓ 38% AUC: ↓ 46% ↔ in Lumefantrine peak concentration (C_{max}) and ↓ exposure (AUC) AUC: ↓ 21% ↔ in Efavirenz peak concentration (C_{max}) and ↓ exposure (AUC) AUC: ↓ 17% C_{max}: ↔ (CYP3A4 induction)	Since decreased concentrations of artemether, dihydroartemisinin, or lumefantrine may result in a decrease of antimalarial efficacy, caution is recommended when TRENVIR and artemether/lumefantrine tablets are co- administered.
Antimalarials: Artemether/lumefantrine/emtricitabine	Interaction not studied.	
Antimalarials	Interaction not studied.	

Artemether/lumefantrine/tenofovir disoproxil		
Antimalarials Atovaquone and proguanil hydrochloride/efavirenz (250/100 mg single dose/600 mg q.d.)	↓ Atovaquone peak concentration (C_{max}) and exposure (AUC) C_{max}: ↓ 44% (↓ 20 to ↓ 61) AUC: ↓ 75% (↓ 62 to ↓ 84) ↔ in Proguanil peak concentration (C_{max}) and ↓ exposure (AUC) AUC: ↓ 43% (↓ 7 to ↓ 65)	Concomitant administration of atovaquone/proguanil with TRENVIR should be avoided.
Antimalarials Atovaquone and proguanil hydrochloride/emtricitabine	Interaction not studied.	
Antimalarials Atovaquone and proguanil hydrochloride/tenofovir disoproxil	Interaction not studied.	
Calcium channel blockers: Diltiazem	↓ Diltiazem concentration ↓ Desacetyl diltiazem concentration	Diltiazem dose adjustments should be guided by clinical response (refer to professional information for diltiazem) No

Others (e.g. felodipine, nicardipine, nifedipine, verapamil)	↓N-monodes-methyl diltiazem concentration ↓Calcium channel blocker	dose adjustment of TRENVIR is necessary when administered with diltiazem. No data are available on the potential interactions of efavirenz with other calcium channel blockers that are substrates of the CYP3A4 enzyme. The potential exists for reduction in plasma concentrations of the calcium channel blocker. Dose adjustments should be guided by clinical response (refer to the Professional Information for the calcium channel blocker)
Calcium channel blockers: Diltiazem/Efavirenz (240 mg q.d./600 mg q.d.)	↓ Diltiazem peak concentration (C_{max}), trough concentration (C_{min}), and exposure (AUC) AUC: ↓ 69% (↓ 55 to ↓ 79)	Dose adjustments of diltiazem when co-administered with TRENVIR should be guided by clinical response (refer to the Summary of Product Characteristics for diltiazem).

	C_{max}: ↓ 60% (↓ 50 to ↓ 68) C_{min}: ↓ 63% (↓ 44 to ↓ 75) ↓ Desacetyl diltiazem peak concentration (C_{max}), trough concentration (C_{min}), and exposure (AUC) AUC: ↓ 75% (↓ 59 to ↓ 84) C_{max}: ↓ 64% (↓ 57 to ↓ 69) C_{min}: ↓ 62% (↓ 44 to ↓ 75) ↓ N-monodesmethyl diltiazem peak concentration (C_{max}), trough concentration (C_{min}), and exposure (AUC) C_{max}: ↓ 28% (↓ 7 to ↓ 44) C_{min}: ↓ 37% (↓ 17 to ↓ 52) AUC: ↓ 37% (↓ 17 to ↓ 52) ↑ Efavirenz peak concentration (C_{max}),	

	trough concentration (C_{min}), and exposure (AUC) C_{max}: ↑ 16% (↑ 6 to ↑ 26) C_{min}: ↑ 13% (↑ 1 to ↑ 26) AUC: ↑ 11% (↑ 5 to ↑ 18) (CYP3A4 induction) The increase in efavirenz pharmacokinetic parameters is not considered clinically significant.	
Calcium channel blockers: Diltiazem/emtricitabine	Interaction not studied.	
Calcium channel blockers: Diltiazem/tenofovir disoproxil	Interaction not studied.	
Calcium channel blockers: Verapamil, felodipine, nifedipine, and nicardipine	Interaction not studied with efavirenz, emtricitabine, or tenofovir disoproxil. When efavirenz is co-administered with a calcium channel blocker that is a substrate of the CYP3A4 enzyme, there	Dose adjustments of calcium channel blockers when co-administered with TRENVIR should be guided by clinical response (refer to the Summary of Product Characteristics for the calcium channel blocker).

	is a potential for reduction in the plasma concentrations of the calcium channel blocker.	
HMG-CoA reductase inhibitors: Atorvastatin, Pravastatin, and Simvastatin	↓ Atorvastatin, pravastatin, and simvastatin concentration	Plasma concentrations of atorvastatin, pravastatin, and simvastatin decreased with efavirenz. Consult the Professional Information for the HMG-CoA reductase inhibitor for guidance on individualising dose.
HMG-CoA reductase inhibitors: Atorvastatin/efavirenz (10 mg q.d./600 mg q.d.)	↓ Atorvastatin peak concentration (C_{max}) and exposure (AUC) C_{max}: ↓ 12% (↓ 1 to ↓ 26) AUC: ↓ 43% (↓ 34 to ↓ 50) ↓ 2-hydroxy atorvastatin peak concentration (C_{max}) and exposure (AUC) C_{max}: ↓ 13% (↓ 0 to ↓ 23) AUC: ↓ 35% (↓ 13 to ↓ 40)	Cholesterol levels should be periodically monitored. Dosage adjustments of atorvastatin may be required when co-administered with TRENVIR (refer to the Summary of Product Characteristics for atorvastatin).

	↓ 4-hydroxy atorvastatin peak concentration (C_{max}) and exposure (AUC) C_{max}: ↓ 47% (↓ 9 to ↓ 51) AUC: ↓ 4% (↓ 0 to ↓ 31) ↓ Total active HMG Co-A reductase inhibitors peak concentration (C_{max}) and exposure (AUC) C_{max}: ↓ 20% (↓ 2 to ↓ 26) AUC: ↓ 34% (↓ 21 to ↓ 41)	
HMG-CoA reductase inhibitors: Atorvastatin/emtricitabine	Interaction not studied.	
HMG-CoA reductase inhibitors: Atorvastatin/tenofovir disoproxil	Interaction not studied.	
HMG-CoA reductase inhibitors: Pravastatin/efavirenz (40 mg q.d./600 mg q.d.)	↓ Pravastatin peak concentration (C_{max}) and exposure (AUC) C_{max}: ↓ 18% (↓ 59 to ↑ 12)	Cholesterol levels should be periodically monitored. Dosage adjustments of pravastatin may be required when co-administered with TRENVIR

	AUC: ↓ 40% (↓ 26 to ↓ 57)	(refer to the Summary of Product Characteristics for pravastatin).
HMG-CoA reductase inhibitors: Pravastatin/Emtricitabine	Interaction not studied.	
HMG-CoA reductase inhibitors: Pravastatin/tenofovir disoproxil	Interaction not studied.	
HMG-CoA reductase inhibitors: Simvastatin/efavirenz	↓ Simvastatin peak concentration (C_{max}) and exposure (AUC) C_{max}: ↓ 76% (↓ 63 to ↓ 79) AUC: ↓ 69% (↓ 62 to ↓ 73) ↓ Simvastatin acid peak concentration (C_{max}) and exposure (AUC) C_{max}: ↓ 51% (↓ 32 to ↓ 58) AUC: ↓ 58% (↓ 39 to ↓ 68) Total active HMG Co-A reductase inhibitors:	Cholesterol levels should be periodically monitored. Dosage adjustments of simvastatin may be required when co-administered with TRENVIR (refer to the Summary of Product Characteristics for simvastatin).

	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.	
HMG-CoA reductase inhibitors: Simvastatin/emtricitabine	Interaction not studied.	
HMG-CoA reductase inhibitors: Simvastatin/tenofovir disoproxil	Interaction not studied.	
HMG-CoA reductase inhibitors: Rosuvastatin/efavirenz	Interaction not studied. Rosuvastatin is largely excreted unchanged via the faeces, therefore interaction with efavirenz is not expected.	TRENVIR and rosuvastatin can be co-administered without dose adjustment.
HMG-CoA reductase inhibitors:	Interaction not studied.	

Rosuvastatin/emtricitabine		
HMG-CoA reductase inhibitors: Rosuvastatin/tenofovir disoproxil	Interaction not studied.	
Narcotic analgesic: Methadone/efavirenz (35-100 mg q.d./600 mg q.d.)	↓ Methadone peak concentration (C_{max}) and exposure AUC: ↓ 52% (↓ 33 to ↓ 66) C_{max}: ↓ 45% (↓ 25 to ↓ 59) (CYP3A4 induction)	Co-administration of efavirenz in HIV-infected individuals with a history of injection medicine use resulted in decreased plasma levels of methadone and signs of opiate withdrawal. Methadone dose was increased by a mean of 22 % to alleviate withdrawal symptoms. Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms. Concomitant administration with TRENVIR should be avoided due to the risk for QTc prolongation (see **section 4.3**).
Narcotic analgesic: Methadone/tenofovir disoproxil (40-110 mg q.d./245 mg q.d.)	↔ in methadone peak concentration (C_{max}), trough	Concomitant administration with TRENVIR should be avoided

	concentration (C_{min}), and exposure (AUC) ↔ in tenofovir concentration peak concentration (C_{max}), trough concentration (C_{min}), and exposure (AUC)	due to the risk for QTc prolongation (see **section 4.3**).
Narcotic analgesic: Methadone/emtricitabine	Interaction not studied.	
Narcotic analgesic: Buprenorphine/naloxone/ Efavirenz	↓ Buprenorphine exposure (AUC) AUC: ↓ 50% ↓ Norbuprenorphine exposure (AUC) AUC: ↓ 71% ↓ Efavirenz exposure (AUC) No clinically significant pharmacokinetic interaction with Efavirenz.	Despite the decrease in buprenorphine exposure, no patients exhibited withdrawal symptoms. Dose adjustment of buprenorphine may not be necessary when co-administered with TRENVIR.
Narcotic analgesic: Buprenorphine/naloxone/emtricitabine	Interaction not studied.	

Narcotic analgesic: Buprenorphine/naloxone/tenofovir disoproxil	Interaction not studied.	
Hormonal contraceptive: Oral ethinyl oestradiol	↑ Ethinyl oestradiol concentration	Clinical significance unknown. Because the potential interaction of efavirenz with oral contraceptives has not been fully characterised, a reliable method of barrier contraception should be used in addition to oral contraceptives.
Hormonal contraceptive: Oral - Ethinyloestradiol + Norgestimate/Efavirenz (0.035 mg + 0.25 mg q.d./600 mg q.d.)	↔ in Ethinyloestradiol peak concentration (C_{max}) and exposure (AUC), and trough concentration (C_{min}) C_{min}: ↓ 8% (↑ 14 to ↓ 25) ↓ Norelgestromin (active metabolite) peak concentration (C_{max}), trough concentration (C_{min}), and exposure (AUC) C_{max}: ↓ 46% (↓ 39 to ↓ 52)	A reliable method of barrier contraception must be used in addition to hormonal contraceptives (see **section 4.6**).

	C_{min}: ↓ 82% (↓ 79 to ↓ 85) AUC: ↓ 64% (↓ 62 to ↓ 67) ↓ Levonorgestrel (active metabolite) peak concentration (C_{max}), trough concentration (C_{min}), and exposure (AUC) C_{max}: ↓ 80% (↓ 77 to ↓ 83) C_{min}: ↓ 86% (↓ 80 to ↓ 90) AUC: ↓ 83% (↓ 79 to ↓ 87) (induction of metabolism) Efavirenz: no clinically significant interaction. The clinical significance of these effects is not known.	
Hormonal contraceptive: Ethinyloestradiol/Tenofovir disoproxil (-/245 mg q.d.)	↔ in Ethinyloestradiol peak concentration (C_{max}) and exposure (AUC)	

	↔ in Tenofovir peak concentration (C_{max}) and exposure (AUC)	
Hormonal contraceptive: Norgestimate/ethinyloestradiol/ emtricitabine	Interaction not studied.	
Hormonal contraceptive: 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	Because of the limited information available, a reliable method of barrier contraception must be used in addition to hormonal contraceptives (see **section 4.6**).

	subjects receiving efavirenz and DMPA remained low consistent with suppression of ovulation.	
Hormonal contraceptive: DMPA/tenofovir disoproxil	Interaction not studied.	
Hormonal contraceptive: DMPA/emtricitabine	Interaction not studied.	
Hormonal contraceptive: 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**).
Hormonal contraceptive: Etonogestrel/tenofovir disoproxil	Interaction not studied.	
Hormonal contraceptive: Etonogestrel/emtricitabine	Interaction not studied.	
Immunosuppressants:	Interaction not studied.	

Immunosuppressants metabolised by CYP3A4 (e.g. cyclosporine, tacrolimus, sirolimus)/efavirenz	↓ 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 TRENVIR.
Immunosuppressants: Tacrolimus/emtricitabine/tenofovir disoproxil (0.1 mg/kg q.d./200 mg/245 mg q.d.)	↔ in tacrolimus peak concentration (C_{max}), concentration at 24 h (C_{24h}), and exposure ↔ in emtricitabine peak concentration (C_{max}), concentration at 24 h (C_{24h}), and exposure No change in tenofovir disoproxil peak concentration (C_{max}), concentration at 24 h (C_{24h}), and exposure	

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.

4.6 Fertility, pregnancy, and lactation

Women of childbearing potential / Contraception in males and females

Pregnancy should be avoided in women receiving TRENVIR.

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

Women of childbearing potential should undergo pregnancy testing prior to initiation of TRENVIR (see **section 4.3**).

Pregnancy

Efavirenz is teratogenic and may cause foetal harm when administered during the first trimester of pregnancy. There have been reports of congenital abnormalities including neural tube defects and meningomyelocele in babies exposed *in utero* to efavirenz during the first trimester of pregnancy. The use of TRENVIR during pregnancy is not recommended as safety and efficacy have not been established (see **section 4.3**).

If this medicine is used during the first trimester of pregnancy, or if the patient becomes pregnant while taking this medicine, the patient should be informed of the potential harm to the foetus. The possibility of termination of pregnancy should be considered and discussed with both patients if there is already evidence of severe harm to the foetus. If termination is unavoidable the patient should be treated with an alternative medicine, known to be safe or safer for use in pregnancy. If no safe or safer alternative is available, cannot be tolerated, has failed or is contraindicated, both partners should be counselled and written consent preferable to both partners be obtained to continue treatment with TRENVIR.

If a patient is to be treated with TRENVIR, pregnancy should be excluded 24 hours prior to initiation of treatment. A medically/laboratory supervised pregnancy/urine test should be done to

exclude pregnancy and repeated at frequent intervals during treatment to exclude pregnancy. Late onset neurological disorders relating to mitochondrial dysfunction have been observed in children who have been exposed *in utero* and/or postnatally to nucleoside analogues as contained in TRENVIR. Studies of efavirenz in animals have shown reproductive toxicity including marked teratogenic effects. There are no adequate and well-controlled studies of TRENVIR in pregnant women.

Breastfeeding

HIV-infected mothers should not breast feed their infants to avoid risking postnatal transmission of HIV. It is not known whether efavirenz, emtricitabine or tenofovir are excreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast feed if they are receiving TRENVIR**.

Fertility

There are no adequate and well-controlled studies of efavirenz, emtricitabine and tenofovir as in TRENVIR in 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.

Efavirenz and therefore TRENVIR may cause dizziness, impaired concentration, and/or drowsiness/somnolence. Patients should be instructed that, if they experience these symptoms, they should avoid potentially hazardous tasks, such as driving or operating machinery.

4.8 Undesirable effects

b) Summary of adverse reactions

Side effects associated with the use of TRENVIR active ingredients

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

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

Less frequent events of renal impairment, renal failure, 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 TRENVIR (see **section 4.4**).

Discontinuation of TRENVIR 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 TRENVIR with food may increase efavirenz exposure and may lead to an increase in the frequency of adverse reactions (see **sections 4.4**).

Tabulated list of adverse reactions

Adverse reactions that may result from a fixed-dose combination tablet of efavirenz, emtricitabine and tenofovir TRENVIR which are not associated with the individual components of the combination product include:

Frequent

- anorexia
- sinusitis,
- upper respiratory tract infections,
- nasopharyngitis
- Immune reconstitution syndrome
- depression,
- insomnia,
- abnormal dreams
- somnolence,
- headache,
- dizziness
- nausea,
- diarrhoea,
- vomiting
- rash

Less frequent

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

Frequency Unknown

- Cushingoid appearance,
- accumulation of body fats,
- dorsocervical fat enlargement (buffalo hump).
- fatigue
- laboratory abnormalities related to fasting cholesterol, creatinine kinase, serum amylase, alkaline phosphatise, aspartate transaminase (AST). Alanine transaminase (ALT), haemoglobin, hyperglycaemia, haematuria, neutrophils, fasting triglycerides, hyper-triglyceridaemia, hypercholesterolaemia, insulin resistance, hyperlactataemia, hyperlipidaemia.

Adverse reactions that may result associated with individual components efavirenz, emtricitabine and tenofovir disoproxil as in TRENVIR are listed in Table 4.

Table 4: Adverse reactions associated with the individual components of efavirenz, emtricitabine and tenofovir disoproxil as in TRENVIR

	Efavirenz	Emtricitabine	Tenofovir disoproxil
Blood and lymphatic system disorders			
Frequent		neutropenia	
Less frequent		anaemia[1]	
Frequency unknown			neutropenia, anaemia
Immune system disorders			
Frequent		allergic reaction	
Less frequent	hypersensitivity		
Frequency unknown	immuno-allergic liver injury/failure	immuno-allergic liver injury/failure	allergic reaction (including angioedema)
Endocrine disorder			
Frequency unknown		sweating, and nephrogenic diabetes insipidus	sweating, and nephrogenic diabetes insipidus

Metabolism and nutrition disorders			
Frequent	hypertriglyceridaemia[3]	lactic acidosis, usually associated with severe hepatomegaly and steatosis, has been associated with nucleoside reverse transcriptase inhibitors, hypertriglyceridemia, hyperglycaemia, and anorexia	hypophosphatemia[2], hypertriglyceridemia, hyperglycaemia, and hypokalaemia, anorexia
Less frequent	hypercholesterolaemia[3]		hypokalaemia[2] and lactic acidosis, usually associated with severe hepatomegaly and steatosis
Frequency unknown	redistribution /accumulation of body fat, anorexia		
Psychiatric disorders			
Frequent	depression (severe in 1.6%)[3], anxiety[3], abnormal dreams[3], insomnia[3], impaired concentration, somnolence, amnesia, euphoria, and confusion	asthenia, anxiety, abnormal dreams, insomnia, and depression	Insomnia, abnormal dreams, depression, asthenia, anxiety, and headaches
Less frequent	suicide attempt[3], suicide ideation[3], psychosis[3], mania[3], paranoia[3], hallucination[3], euphoric mood[3], affect lability[3], confusional state[3], aggression[3], catatonia[3] completed suicide[3,4], delusion[3,4], neurosis[3,4], and hypoesthesia	dizziness, neuritis, paraesthesia, and peripheral neuropathy	Anorexia
Frequency unknown	suicidal thoughts or attempts, delusion, neurosis, ataxia, paraesthesia, hyper-somnolence, encephalopathy, coma, agitation, neuropathy, tremors, apathy, neuralgia,		peripheral neuropathy, and anxiety

	peripheral neuropathy, and speech disorder		
Nervous System Disorders			
Frequent	cerebellar coordination and balance disturbances[3], somnolence (2.0%)[3], headache (5.7%)[3], disturbance in attention (3.6%)[3], dizziness (8.5%), and insomnia	headache dizziness, and somnolence	dizziness, headache, paraesthesia, peripheral neuropathy, anxiety, insomnia, and somnolence
Less frequent	convulsions[3], amnesia[3], thinking abnormal[3], ataxia[3], coordination abnormal[3], agitation[3], and tremor		
Frequency unknown	hypoaesthesia abnormal coordination neuropathy, depersonalisation and nervousness		
Eye Disorders			
Less frequent	blurred vision		
Ear and labyrinth disorders			
Less frequent	tinnitus and vertigo		
Cardiac disorders			
Frequency unknown	palpitations and tachycardia		
Vascular disorders			
Less frequent	flushing		
Respiratory, thoracic and mediastinal disorders			
Frequent		increased cough, rhinitis, and pneumonia	cough, rhinitis, and pneumonia
Less frequent		dyspnoea	dyspnoea
Frequency unknown	dyspnoea, asthma, sinusitis, and upper respiratory tract infections		chest pain
Gastrointestinal disorders			
Frequent	diarrhoea, vomiting, abdominal pain, nausea, and dyspepsia	diarrhoea, nausea, elevated amylase including elevated pancreatic amylase,	diarrhoea, vomiting, nausea, abdominal pain, abdominal distension, flatulence, and dyspepsia

		elevated serum lipase, vomiting, abdominal pain, and dyspepsia flatulence	
Less frequent	pancreatitis		raised serum amylase concentrations, pancreatitis
Frequency unknown	gastritis, gastroenteritis, gastro-oesophageal reflux, constipation malabsorption, taste perversion, and increased appetite.		
Hepatobiliary disorders			
Frequent	elevated aspartate aminotransferase (AST), elevated alanine aminotransferase (ALT), and elevated gammaglutamyltransferase (GGT)	elevated serum AST and/or elevated serum ALT, and hyperbilirubinaemia	hepatotoxicity, including lactic acidosis, and increased transaminases (AST and ALT)
Less frequent	Hepatitis, acute and hepatic failure[3,4]	hepatotoxicity	raised liver enzymes, hepatic steatosis, and hepatitis
Frequency unknown		hepatitis	
Skin and subcutaneous tissue disorders			
Frequent	rash (moderate-severe, 11.6%, all grades, 18%)[3], pruritus, and increased sweating		skin rashes (including rash, pruritus)
Less frequent	Stevens-Johnson syndrome, erythema multiforme[3], severe rash (<1%), and photoallergic dermatitis	vesiculobullous rash, pustular rash, maculopapular rash, rash, pruritus, urticaria, allergic reaction, and skin discolouration, manifested by hyperpigmentation on the palms and/or soles (generally mild) and angioedema[1]	rash, maculopapular rash, urticaria, vesiculobullous rash, pustular rash, hyper-pigmentation of soles and/or palms, and angioedema
Frequency unknown	flushing, nail disorders, skin discolouration,		pruritus

	acne, alopecia, eczema, folliculitis, seborrhoea, skin exfoliation, urticaria, and nail disorders		
Musculoskeletal, connective tissue, and bone disorders			
Frequent		back pain and elevated creatine kinase	back pain
Less frequent		arthralgia, myalgia, bone pain, osteomalacia, and myopathy.	rhabdomyolysis[2], muscular weakness[2], myalgia, arthralgia osteomalacia (manifested as bone pain and infrequently contributing to fractures)[2,4], and myopathy[2]
Frequency unknown	Arthralgia, myalgia, and myopathy		Bone density decreased (see **section 4.4**)
Renal and urinary disorders			
Frequent		elevation of creatinine kinase	increased creatinine kinase levels, proteinuria, proximal renal tubulopathy including Fanconi syndrome, renal failure (acute and chronic), acute tubular necrosis, nephritis (including acute interstitial nephritis)[4], and nephrogenic diabetes insipidus
Less frequent			
Frequency unknown		nephritis, acute renal failure, renal impairment, Fanconi's syndrome, acute tubular necrosis, polyuria, and proximal renal tubulopathy	Polyuria and renal insufficiency
Reproductive system and breast disorders			
Less frequent	gynaecomastia		
Frequency unknown	impotence, decreased libido, and increased libido	breast enlargement	breast enlargement
General disorders and administration site conditions			

Frequent	fatigue and pain	pain, asthenia, and fatigue	Asthenia and fatigue
Frequency unknown	asthenia, alcohol intolerance, allergic reaction, hot flushes, influenza-like symptoms, malaise, pain, syncope, and redistribution/accumulation of body fat.		fever, sweating, weight loss and fatigue
Investigations			
Frequency unknown		elevations of bilirubin, pancreatic amylase, serum glucose, urine glucose, raised serum amylase, hypophosphatemia, and raised liver enzymes	elevations of bilirubin, pancreatic amylase, serum glucose, urine glucose, raised serum amylase, hypophosphatemia, and raised liver enzymes

1 Anaemia and skin discolouration (increased pigmentation) were frequent when emtricitabine was administered to paediatric patients.

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

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

4 This adverse reaction was identified through post-marketing surveillance for either efavirenz, emtricitabine or tenofovir disoproxil. The frequency category was estimated from a statistical calculation based on the total number of patients treated with efavirenz in clinical trials (n = 3,969) or exposed to emtricitabine in randomised controlled clinical trials (n = 1,563) or exposed to tenofovir disoproxil in randomised controlled clinical trials and the expanded access programme (n = 7,319).

Description of selected adverse reactions

Rash

In studies of efavirenz, rashes were usually mild-to-moderate maculopapular skin eruptions that

occurred within the first two weeks of initiating therapy with efavirenz. In most patients the rash resolved with continuing therapy with efavirenz within one month. TRENVIR can be reinitiated in patients interrupting therapy because of rash. Use of appropriate antihistamines and/or corticosteroids is recommended when TRENVIR is restarted.

Psychiatric symptoms

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

Nervous system symptoms

Nervous system symptoms are common with efavirenz, one of the components of TRENVIR. In 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 TRENVIR is taken concomitantly with meals possibly due to increased efavirenz plasma levels. 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 TRENVIR may cause renal damage, monitoring of renal function is recommended (see **sections 4.4** and **4.8 Summary of the safety profile**). Proximal renal tubulopathy generally

resolved or improved after tenofovir disoproxil discontinuation. However, in some patients, declines in creatinine clearance did not completely resolve despite tenofovir disoproxil discontinuation.

Patients at risk of renal impairment (such as patients with baseline renal risk factors, advanced HIV disease, or patients receiving concomitant nephrotoxic medications) are at increased risk of experiencing incomplete recovery of renal function despite tenofovir disoproxil discontinuation (see **section 4.4**).

Interaction with didanosine

Co-administration of tenofovir, emtricitabine and efavirenz as in TRENVIR and didanosine is not recommended as it results in a 40 to 60 % increase in systemic exposure to didanosine that may increase the risk of didanosine-related adverse reactions (see **section 4.5***)*. Pancreatitis and lactic acidosis, sometimes fatal, have been less frequently reported.

Lactic acidosis

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

Metabolic parameters

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

Immune Reconstitution Inflammatory Syndrome

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

Osteonecrosis

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

Paediatric population

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

Other special populations

Elderly

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

Patients with renal impairment

Since tenofovir disoproxil can cause renal toxicity, close monitoring of renal function is recommended in any patient with mild renal impairment treated with TRENVIR (see **sections 4.2**, **4.4**).

HIV/HBV or HCV co-infected patients

The adverse reaction profile of efavirenz, emtricitabine and tenofovir disoproxil in patients co-infected with HIV/HBV or HIV/HCV is 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 occur 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**).

Laboratory abnormalities

Raised liver enzyme values have occurred, particularly in patients with viral hepatitis. Raised serum cholesterol and triglyceride concentrations have been reported.

Liver enzymes

Elevations of AST and ALT to greater than five times the upper limit of the normal range were seen in patients treated with 600 mg of efavirenz. Elevations of GGT in patients receiving efavirenz may reflect enzyme induction not associated with liver toxicity (see **section 4.4**).

Lipids

Increases in total cholesterol of 10 to 20 % have been observed in some uninfected volunteers receiving efavirenz. Increases in non-fasting total cholesterol and HDL of approximately 20 % and 25 %, respectively, were observed in patients treated with efavirenz + ZDV + 3TC and of approximately 40 % and 35 %, in patients treated with efavirenz + IDV. The effects of efavirenz

on triglycerides and LDL were not well characterised. The clinical significance of these findings is unknown (see **section 4.4**).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website or to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

If overdose occurs, the patient must be monitored for evidence of toxicity (see **section 4.8**), including monitoring of vital signs and observation of the patient's clinical status, and standard supportive treatment applied as necessary.

Emtricitabine

Limited clinical experience is available at doses higher than the therapeutic dose of emtricitabine (200 mg). No adverse reactions were reported when single doses of emtricitabine 1 200 mg were administered to patients in a clinical study.

Haemodialysis treatment removes approximately 30 % of the emtricitabine dose over a 3-hour dialysis period starting within 1,5 hours of emtricitabine dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min). It is not known whether emtricitabine can be removed by peritoneal dialysis.

Tenofovir disoproxil fumarate

Limited clinical experience at doses higher than the therapeutic dose of tenofovir 300 mg is available. No severe adverse reactions were reported when tenofovir disoproxil fumarate 600 mg was administered orally to patients for 28 days. The effects of higher doses are not known.

Tenofovir is efficiently removed by haemodialysis with an extraction coefficient of approximately 54 %. Following a single 300 mg dose of tenofovir, a 4-hour haemodialysis session removed approximately 10 % of the administered tenofovir dose.

Efavirenz

Some patients accidentally taking 600 mg twice daily have reported increased nervous system symptoms and involuntary muscle contractions. Treatment of overdose with efavirenz should consist of general supportive measures, including monitoring of vital signs and observation of the patient's clinical status. Administration of activated charcoal may be used to aid removal of unabsorbed medicine. There is no specific antidote for overdose with efavirenz. Since efavirenz is highly protein bound, dialysis is unlikely to significantly remove the medicine from the blood.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 20.2.8 Antimicrobial (chemotherapeutic) agents. Antiviral agents.

Pharmacotherapeutic group: Antivirals for treatment of HIV infections, combinations.

ATC code: J05AR06

Mechanism of action

TRENVIR is a fixed dose combination tablet containing efavirenz, emtricitabine and tenofovir disoproxil fumarate (tenofovir DF). Efavirenz is a non-nucleoside reverse transcriptase inhibitor, emtricitabine is a synthetic nucleoside analogue of cytidine, and tenofovir DF is converted in vivo

to tenofovir, an acyclic nucleoside phosphonate (Nucleotide) analogue of adenosine 5'-monophosphate.

Emtricitabine

Emtricitabine, a NRTI, is a synthetic nucleoside analogue of cytidine. It is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the human immunodeficiency virus type 1 (HIV-1) reverse transcriptase (RT) by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine 5'-triphosphate is a weak inhibitor of mammalian DNA polymerase α, β, ε and mitochondrial DNA polymerase γ.

Tenofovir disoproxil fumarate

Tenofovir disoproxil fumarate, a NRTI, also known as tenofovir DF, is an acyclic nucleoside phosphonate diester analogue of adenosine monophosphate. Tenofovir disoproxil fumarate requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylation's by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 RT by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Efavirenz

Efavirenz is a selective non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. Efavirenz diffuses into the cell where it binds adjacent to the active site of reverse transcriptase. This produces a conformational change in the enzyme and inhibits its function. Efavirenz is a non-competitive inhibitor of HIV-1 reverse transcriptase (RT) with respect to template, primer or

nucleoside triphosphates, with a small component of competitive inhibition. HIV-2 RT and human cellular DNA polymerases alpha, beta, gamma, and delta are not inhibited by concentrations of efavirenz.

Pharmacodynamics

Antiviral activity

Efavirenz, emtricitabine and tenofovir disoproxil fumarate:

In combination studies evaluating the *in vitro* antiviral activity of emtricitabine and tenofovir together, emtricitabine and efavirenz together and efavirenz and tenofovir together, synergistic antiviral effects were observed.

Emtricitabine

The *in vitro* activity of emtricitabine against laboratory and clinical isolates of HIV was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. The IC_{50} (50 % inhibitory concentration) values for emtricitabine were in the range of 0,0013 to 0,64 µM (0,0003 to 0,158 µg/mL). In medicine combination studies of emtricitabine with nucleoside reverse transcriptase inhibitors (abacavir, lamivudine, stavudine, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Most of these medicine combinations have not been studied in humans. Emtricitabine displayed antiviral activity *in vitro* against HIV-1 clades A, B, C, S, E, F and G (IC_{50} values ranged from 0,007 to 0,075 µM) and showed strain specific activity against HIV-2 (IC_{50} values ranged from 0,007 to 1,5 µM).

Tenofovir disoproxil fumarate

The *in vitro* antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The IC_{50} values for tenofovir were in the range of 0,04 to 8,5 µM. In medicine combination studies of tenofovir with nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Tenofovir displayed antiviral activity *in vitro* against HIV-1 clades A, B, C, D, E, F, G and O (IC_{50} values ranged from 0,5 to 2,2 µM). The IC_{50} values of tenofovir against HIV-2 ranged from 1,6 µM to 4,9 µM.

Efavirenz

The clinical significance of *in vitro* susceptibility of HIV-1 to efavirenz has not been established. The *in vitro* antiviral activity of efavirenz was assessed in lymphoblastoid cell lines, peripheral blood mononuclear cells (PBMCs) and macrophage/monocyte cultures enriched from PBMCs. The 90 to 95 % inhibitory concentration (IC_{90-95}) of efavirenz for wild type laboratory adapted strains and clinical isolates ranged from 1,7 to 25 nM. Efavirenz demonstrated additive antiviral activity against HIV-1 in cell culture when combined with non-nucleoside reverse transcriptase inhibitors (NNRIs) (nevirapine and delavirdine) nucleoside reverse transcriptase inhibitors (NRTIs) (abacavir, didanosine, lamivudine, stavudine, zalcitabine and zidovudine), protease inhibitors (PIs) (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir and saquinavir) and the fusion inhibitor enfuvirtide. Efavirenz demonstrated additive to antagonistic antiviral activity in cell culture with atazanavir. 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. Efavirenz is not active against HIV-2.

Drug resistance

Emtricitabine, tenofovir disoproxil fumarate and efavirenz

HIV-1 isolates with reduced susceptibility to the combination of emtricitabine and tenofovir have been selected *in vitro*. Genotypic analysis of these isolates identified the M184I/V and/or K65R amino acid substitutions in the viral RT.

Emtricitabine

Emtricitabine-resistant isolates of HIV have been selected *in vitro*. Genotypic analysis of these isolates showed that the reduced susceptibility to emtricitabine was associated with a mutation in the HIV RT gene at codon 184 which resulted in an amino acid substitution of methionine by valine or isoleucine (M184V/I).

Emtricitabine-resistant isolates of HIV have been recovered from some patients treated with emtricitabine alone or in combination with other antiretroviral medicines. Genotypic analysis of these isolates showed that the resistance was due to M184V/I mutations in the HIV RT gene.

Tenofovir disoproxil fumarate

HIV-1 isolates with reduced susceptibility to tenofovir have been selected *in vitro*. These viruses expressed a K65R mutation in RT and showed a 2- to 4-fold reduction in susceptibility to tenofovir. Tenofovir-resistant isolates of HIV-1 have also been recovered from some patients treated with tenofovir in combination with certain antiretroviral medicines. Genotypic analysis of the resistant isolates showed a mutation in the HIV-1 RT gene resulting in the K65R amino acid substitution.

Efavirenz

HIV-1 isolates with reduced susceptibility to efavirenz (greater than 380-fold increase in IC_{90}) compared to baseline can emerge *in vitro*. Phenotypic changes in evaluable HIV-1 isolates and genotypic changes in plasma virus from selected patients treated with efavirenz in combination with IDV or with ZDV plus lamivudine were monitored. One or more RT mutations at amino acid

positions 100, 101, 103, 108, 190 and 225 were observed in all 62 patients with a frequency of at least 10 % compared to baseline. The mutation at RT amino acid position 103 (lysine to asparagine) was the most frequently observed (greater or equal to 90 %). A mean loss in susceptibility (IC_{90}) to efavirenz of 47-fold was observed in 26 clinical isolates. Five clinical isolates were evaluated for both genotypic and phenotypic changes from baseline. Decreases in efavirenz susceptibility (range from 9- to greater than 312-fold increase in IC_{90}) were observed for these isolates *in vitro* compared to baseline. All 5 isolates possessed at least one of the efavirenz-associated RT mutations. The clinical relevance of phenotypic and genotypic changes associated with efavirenz therapy has not been established.

Cross-resistance

Emtricitabine, tenofovir disoproxil fumarate and efavirenz

Cross-resistance among certain nucleoside reverse transcriptase inhibitors (NRTIs) has been recognised. The M184V/I and/or K65R substitutions selected *in vitro* by the combination of emtricitabine and tenofovir are also observed in some HIV-1 isolates from subjects failing treatment with tenofovir in combination with either lamivudine or emtricitabine, and either abacavir or didanosine. Therefore, cross-resistance among these medicines may occur in patients whose virus harbours either or both of these amino acid substitutions.

Emtricitabine

Emtricitabine-resistant isolates (M184V/I) were cross-resistant to lamivudine and zalcitabine, but retained susceptibility *in vitro* to didanosine, stavudine, tenofovir, zidovudine, and NNRTIs (delavirdine, efavirenz, and nevirapine). Isolates from heavily treatment-experienced patients containing the M184V/I amino acid substitution in the context of other NRTI resistance-associated substitutions may retain susceptibility to tenofovir. HIV-1 isolates containing the K65R substitution, selected *in vivo* by abacavir, didanosine, tenofovir, and zalcitabine, demonstrated

reduced susceptibility to inhibition by emtricitabine. Viruses harbouring mutations conferring reduced susceptibility to stavudine and zidovudine called thymidine analogue mutations (TAMs) (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) or didanosine (L74V) remained sensitive to emtricitabine. HIV-1 containing the K103N substitution associated with resistance to NNRTIs was susceptible to emtricitabine.

Tenofovir disoproxil fumarate

HIV-1 isolates whose HIV-1 expressed a mean of 3 zidovudine-associated RT amino acid substitutions (M41L, D67N, K70R, L210W, T215Y/F or K219Q/E/N) have a decreased susceptibility to tenofovir. Multinucleoside resistant HIV-1 with a T69S double insertion mutation in the RT showed reduced susceptibility to tenofovir.

Efavirenz

Rapid emergence of HIV-1 strains that are cross-resistant to non-nucleoside RT inhibitors has been observed *in vitro*. Clinical isolates previously characterised as efavirenz-resistant were also phenotypically resistant to nevirapine and delavirdine *in vitro* compared to baseline. Clinically derived ZDV-resistant HIV-1 isolated and tested *in vitro* retained susceptibility to efavirenz. Cross-resistance between efavirenz and HIV protease inhibitors is unlikely because of the different enzyme targets involved.

5.2 Pharmacokinetic properties

Adults

Emtricitabine

Following oral administration of emtricitabine (200 mg), emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1 to 2 hours post-dose. *In vitro* binding of emtricitabine to human plasma proteins is < 4 % and is independent of concentration over the range of 0,02 to

200 µg/mL. Median (range) fasted oral bioavailability of emtricitabine is 92 % (83,1 to 106,4 %). Mean (± SD) C_{max} (maximum plasma concentration) of emtricitabine at steady state is 1,8 ± 0,72 µg/mL and mean (± SD) AUC at steady state is 10,0 ± 3,12 µg.hr/mL.

Following administration of radiolabelled emtricitabine, approximately 86 % is recovered in the urine and 13 % is recovered as metabolites. The metabolites of emtricitabine include 3'-sulfoxide diastereomers and their glucuronic acid conjugate. Emtricitabine is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of emtricitabine (200 mg), the plasma emtricitabine half-life is approximately 10 hours.

Tenofovir disoproxil fumarate

Following oral administration of tenofovir, maximum tenofovir serum concentrations are achieved in 1,0 ± 0,4 hour. *In vitro* binding of tenofovir to human plasma proteins is < 0,7 % and is independent of concentration over the range of 0,01 to 25 µg/mL. Median (range) fasted oral bioavailability of tenofovir is 25 % (NC – 45,0 %). Mean (± SD) C_{max} of tenofovir is 0,30 ± 0,09 µg/mL and mean (± SD) AUC is 2,29 ± 0,69 µg.hr/mL.

Approximately 70 to 80 % of an intravenous dose of tenofovir is recovered unchanged in the urine. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of tenofovir, the terminal elimination half-life is approximately 17 hours.

Efavirenz

In HIV-infected patients time-to-peak plasma concentrations were approximately 3 to 5 hours and steady-state plasma concentrations were reached in 6 to 10 days. Efavirenz is highly bound, approximately 99,5 to 99,75 % to human plasma proteins, predominantly albumin. *In vitro* studies suggest CYP3A4 and CYP2B6 are the major isozymes responsible for efavirenz metabolism. Efavirenz has been shown to induce P450 enzymes, resulting in induction of its own metabolism.

Efavirenz has a terminal half-life of 52 to 76 hours after single doses and 40 to 55 hours after multiple doses.

Effects of food on oral absorption

A fixed dose combination of emtricitabine and tenofovir may be administered with or without food. Administration of this fixed dose combination tablet following a high fat meal, or a light meal delayed the time of tenofovir C_{max} by approximately 0,75 hours. The mean increases in tenofovir AUC and C_{max} were approximately 35 % and 15 %, respectively, when administered with a high fat or light meal, compared to administration in the fasted state. In previous safety and efficacy studies, tenofovir was taken under fed conditions. Emtricitabine systemic exposures (AUC and C_{max}) were unaffected when the combination tablet was administered with either a high fat or a light meal.

Special Populations

Gender

Emtricitabine and tenofovir pharmacokinetics are similar in male and female patients. Pharmacokinetics of efavirenz in patients appear to be similar between men and women.

Paediatric and elderly population

Emtricitabine and tenofovir disoproxil fumarate

Pharmacokinetics of emtricitabine and tenofovir have not been evaluated in children < 18 years or in the elderly (> 65 years) (see **section 4.4**).

Efavirenz

Pharmacokinetics of efavirenz have not been studied in subjects aged 65 and over to establish whether they respond differently. The pharmacokinetics of efavirenz in paediatric patients are similar to adults.

Patients with impaired renal function

Emtricitabine and tenofovir disoproxil fumarate

The pharmacokinetics of emtricitabine and tenofovir are altered in patients with renal impairment (see **section 4.4**). In patients with creatinine clearance < 50 mL/min, C_{max}, and $AUC_{0-\alpha}$ of emtricitabine and tenofovir were increased. It is recommended that the dosing interval be modified in patients with creatinine clearance 30 to 49 mL/min. Since this is not possible with a fixed dose combination, such a combination should not be administered to patients with creatinine clearance < 50 mL/min and in patients with end-stage renal disease requiring dialysis (see **section 4.2, 4.3,** and **4.4**).

Efavirenz

The pharmacokinetics of efavirenz have not been studied in patients with renal insufficiency. However, less than 1 % of efavirenz is excreted unchanged in the urine, so the impact of renal impairment on efavirenz elimination should be minimal.

Patients with hepatic impairment

Emtricitabine and tenofovir disoproxil fumarate

The pharmacokinetics of tenofovir following a 300 mg dose of tenofovir disoproxil fumarate have been studied in non-HIV infected patients with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in patients with hepatic impairment compared with unimpaired patients. The pharmacokinetics of emtricitabine or a fixed dose combination of emtricitabine and tenofovir have not been studied in patients with hepatic

impairment. Emtricitabine is not significantly metabolised by liver enzymes, so the impact of liver impairment should be limited.

Efavirenz

The pharmacokinetics of efavirenz have not been adequately studied in patients with hepatic impairment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core Tablet

Corn starch

Croscarmellose sodium

Flexicoat Prot Pink V5 PHA9070

Hydroxy propyl cellulose

Hypromellose

Magnesium stearate

Microcrystalline cellulose

Red oxide of iron

Sodium lauryl sulphate

Coating (Flexicoat Prot Pink V5 PHA9070)

Hexalake Sunset Yellow

Kollicoat Protect

Sicovit Red

Talc

Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 30 °C.

Keep the bottle tightly closed.

Do not use if seal over bottle opening is broken or missing.

6.5 Nature and contents of container

TRENVIR is packed as:

- 28s, 30s, 84s or 90s tablets supplied in a white, opaque, HDPE bottle containing a silica gel bag made from non-woven fabric and closed with a white opaque HDPE grade non-child resistant screw cap, packed in a carton.
- 28s or 30s tablets supplied in a cylindrical milky white or white 100 mL HDPE bottle containing three (3) silica gel bags and closed with a HDPE screw cap with smooth surface on top and ribbed along the height, packed in a carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO MANUFACTURING (PTY) LTD.

1474 South Coast Road

Mobeni

Durban

4052

Customer care: 080 222 6662

8. REGISTRATION NUMBER(S)

44/20.2.8/0780

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorisation: 09 February 2012

Latest renewal: Not applicable.

10. DATE OF REVISION OF THE TEXT

17 July 2026