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). TRENVIR IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION AND THE SAFETY AND EFFICACY OF TRENVIR HAS 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. 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 tablets.

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 health care provider experienced in the management of HIV infection.

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.

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 astemizole, bepridil, cisapride, midazolam, 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.
- 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.

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 / 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.

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 after stopping treatment. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

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 has 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 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.

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. 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. 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. 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.

Medicine interactions *(see* ***section 4.5****)*

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.

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. It is recommended that TRENVIR be taken on an empty stomach, preferably at home.

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**).

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

Seizures

Convulsions have been observed in patients receiving efavirenz, generally in the presence of a known medical history of seizures. Patients who are receiving concomitant anticonvulsant medicines primarily metabolised by the liver, such as carbamazepine, phenytoin, and phenobarbital, may require periodic monitoring of plasma levels.

Renal impairment

Emtricitabine and tenofovir, two of the active ingredients in TRENVIR, are principally eliminated by the kidney. 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**).

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 should be carefully monitored for changes in serum creatinine and phosphorus.

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. 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. 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 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. 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. There have been reports of mitochondrial dysfunction in HIV negative infants exposed *in utero* and/or postnatally to nucleoside analogues. Apart from lactic acidosis/hyperlactataemia (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 child exposed *in utero* to nucleoside and nucleotide analogues, even HIV negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms.

Osteonecrosis

Cases of osteonecrosis have been reported particularly in patient with advanced HIV disease and/or long-term exposure to 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.

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 clinical study through 144 weeks, 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.

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, 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, cytomegalovirus retinitis, and cryptococcal meningitis.

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) 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.

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 must not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, triazolam, pimozide, bepridil or ergot alkaloids, 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.

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.

Efavirenz

The efavirenz in TRENVIR is an inducer of CYP3A4. Other compounds that are substrates of CYP3A4 may have decreased plasma concentrations when co-administered with TRENVIR.

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.

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.

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 (mg)/ Method of administration[1]	Tenofovir method of administration[1]	N	% Difference (90 % CI) vs. 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's

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	Contra-indicated 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	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 sections of respiratory depression.
Calcium channel blocker: Bepridil	Contraindicated due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.
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.
St. John's wort *(Hypericum*	Not recommended: Expected to substantially decrease plasm

perforatum)	levels of efavirenz, has not been studied in combination with efavirenz.

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	↓ Amprenavir 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. TRENVIR should be discontinued in patients who develop tenofovir-associated adverse events.
Protease inhibitor: Ritonavir	↑ Ritonavir concentration ↑ Efavirenz concentration	When ritonavir 50 mg every 12 hours was co-administered with efavirenz 600 mg once daily, the combination was associated with 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.
NRTI: 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.
Other medicines		
Anticoagulant: Warfarin	↑↓ Or ↓ warfarin concentration	Plasma concentrations and effects potentially increased or decreased by efavirenz.
Anticonvulsants: Carbamazepine	↓ Carbamaze-pine concentration Efavirenz ↓ concentration	There are insufficient data to make a dose recommendation for TRENVIR. Alternative anticonvulsant treatment should be used.
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.
Antidepressant: Sertraline	↓ Sertraline concentration	Increases in sertraline dose should be guided by clinical response.
Antifungals: Itraconazole Ketoconazole	↓ Itraconazole concentration ↓ Hydroxy itraconazole concentration ↓ Ketoconazole	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

	concentration	the potential to decrease plasma concentrations of ketoconazole.
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.
Calcium channel blockers: Diltiazem Others (e.g. felodipine, nicardipine, nifedipine, verapamil)	↓ Diltiazem concentration ↓ Desacetyl diltiazem concentration ↓ N-monodes-methyl diltiazem concentration ↓ Calcium channel blocker	Diltiazem dose adjustments should be guided by clinical response. No 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.

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 complete package insert for the HMG-CoA reductase inhibitor for guidance on individualising dose.
Narcotic analgesic: Methadone	↓ Methadone concentration	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.
Oral contraceptive: Ethinyloestradiol	↑ 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.

4.6 Fertility, pregnancy, and lactation

Women of childbearing potential / Contraception in males and females

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 prior to initiation of TRENVIR (see **section 4.3**).

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

Breastfeeding

HIV-infected mothers should not breast feed their infants. 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**.

4.7 Effects on ability to drive and use machines

Efavirenz, and therefore TRENVIR, may cause dizziness, impaired concentration, and/or drowsiness. 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

EMTRICITABINE

Blood and lymphatic system disorders:

Frequency unknown: Neutropenia, anaemia.

Immune system disorders:

Frequent: Allergic reaction.

Frequency unknown: Immuno-allergic liver injury/failure.

Endocrine disorders:

Frequency unknown: Sweating, nephrogenic diabetes insipidus.

Metabolic and nutrition disorders:

Frequent: Lactic acidosis, usually associated with severe hepatomegaly and steatosis, has been associated with nucleoside reverse transcriptase inhibitors. Hypertriglyceridemia and hyperglycaemia, anorexia.

Psychiatric disorders:

Frequent: Asthenia, anxiety.

Abnormal dreams and insomnia

Less frequent: Depressive disorders, dizziness, neuritis, paraesthesia, and peripheral neuropathy.

Nervous system disorders:

Frequent: Headache and dizziness.

Respiratory, thoracic, and mediastinal disorders:

Frequent: Increased cough, rhinitis, pneumonia.

Less Frequent: Dyspnoea.

Gastrointestinal disorders:

Frequent: Nausea, diarrhoea, abdominal pain, dyspepsia, flatulence, vomiting.

Less frequent: Elevated amylase including elevated pancreatic amylase, elevated serum lipase.

Hepato-biliary disorders:

Less frequent: Hepatotoxicity.

Frequency unknown: Raised liver enzyme concentrations and hyperbilirubinemia, hepatitis.

Skin and subcutaneous tissue disorders:

Less frequent: Rash event (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash, and allergic reaction) and skin discolouration, manifested by hyperpigmentation on the palms and/or soles (generally mild) and angioedema.

Musculoskeletal, connective tissue and bone disorders:

Frequent: Back pain.

Less frequent: Arthralgia, myalgia, bone pain, osteomalacia, myopathy.

Renal and urinary disorders:

Frequent: Elevation of creatinine kinase.

Frequency unknown: Nephritis, acute renal failure, renal impairment, Fanconi's syndrome, acute tubular necrosis, polyuria, proximal renal tubulopathy.

Reproductive system and breast disorders:

Frequency unknown: Breast enlargement.

General disorders and administrative site conditions:

Frequent: Pain, asthenia.

Frequency unknown: Fatigue.

Investigations:

Frequency unknown: Elevations of bilirubin, pancreatic amylase, serum glucose, urine glucose, raised serum amylase, hypophosphatemia, raised liver enzymes.

TENOFOVIR:

Blood and lymphatic system disorders:

Frequency unknown: Neutropenia, anaemia.

Immune system disorders:

Frequency unknown: Allergic reactions.

Endocrine disorders:

Frequency unknown: Sweating, nephrogenic diabetes insipidus.

Metabolism and nutrition disorders:

Frequent: Hypophosphatemia, lactic acidosis, usually associated with severe hepatomegaly and steatosis; also, hypertriglyceridemia, hyperglycaemia, and hypokalaemia, anorexia.

Psychiatric disorders:

Frequent: Asthenia, anxiety, headaches.

Less frequent: Anorexia, abnormal dreams.

Frequency unknown: Depression, insomnia, peripheral neuropathy, and anxiety.

Nervous system disorders:

Frequent: Dizziness and headache, paraesthesia, peripheral neuropathy, anxiety, insomnia.

Respiratory, thoracic, and mediastinal disorders:

Frequent: Cough, rhinitis, pneumonia.

Less Frequent: Dyspnoea.

Frequency unknown: Chest pain.

Gastrointestinal disorders:

Frequent: Nausea, vomiting, diarrhoea, abdominal pain, flatulence, dyspepsia.

Less frequent: Raised serum amylase concentrations, pancreatitis.

Hepatobiliary disorders:

Less frequent: Hepatotoxicity, including lactic acidosis, increased transaminases.

Less frequent: Raised liver enzymes, hepatic steatosis, and hepatitis.

Skin and subcutaneous tissue disorders:

Frequent: Skin rashes (including rash, pruritus).

Less Frequent: Maculopapular rash, urticaria, vesiculobullous rash, pustular rash, hyper-pigmentation of soles and/or palms, angioedema.

Musculoskeletal, connective tissue and bone disorders:

Frequent: Back pain

Less frequent: Rhabdomyolysis, muscular weakness, myalgia, arthralgia, osteomalacia (manifested as bone pain and infrequently contributing to fractures), myopathy.

Frequency unknown: Bone density decreased (see **section 4.4**)

Renal and urinary disorders:

Frequency unknown: Increased creatinine kinase levels, nephritis, nephrogenic diabetes insipidus, renal impairment, acute renal failure, and effects on the renal proximal tubules, including Fanconi syndrome and acute tubular necrosis.

Reproductive system and breast disorders:

Frequency unknown: Breast enlargement.

General disorders and administrative site conditions:

Frequent: Asthenia.

Frequency unknown: Fever, sweating, weight loss, fatigue.

Investigations:

Frequency unknown: Elevations of bilirubin, pancreatic amylase, serum glucose, urine glucose, raised serum amylase, hypophosphatemia, raised liver enzymes.

EFAVIRENZ:

Immune system disorders:

Less frequent: Hypersensitivity.

Metabolic and nutritional disorders:

Frequent: Hypertriglyceridemia, hypercholesterolaemia.

Frequency unknown: Weight gain and weight loss, anorexia.

Psychiatric disorders:

Frequent: Insomnia, abnormal dreams, anxiety, depression, impaired concentration, somnolence, amnesia, euphoria, confusion.

Less frequent: Hypoesthesia, suicide attempt, suicide ideation, psychosis, mania, paranoia, hallucination, affect lability, aggression.

Frequency unknown: Suicidal thoughts or attempts, delusion, neurosis, ataxia, paraesthesia, neuropathy, tremors, agitation, apathy, neuralgia, peripheral neuropathy, speech disorder.

Nervous system disorders:

Frequent: Headache, dizziness, insomnia.

Less frequent: Cerebellar coordination and balance disturbances, somnolence, disturbance in attention, convulsion, amnesia, thinking abnormal, ataxia,

coordination abnormal, agitation, tremor, hypoesthesia, depersonalisation, paraesthesia, nervousness.

Eye disorders:

Less frequent: Blurred vision.

Ear and labyrinth disorders:

Less frequent: Tinnitus, vertigo.

Cardiac disorders:

Frequency unknown: Palpitations and tachycardia.

Vascular disorders:

Less frequent: Flushing.

Respiratory, thoracic, and mediastinal disorders:

Frequency unknown: Asthma, sinusitis, dyspnoea, and upper respiratory tract infections.

Gastrointestinal disorders:

Frequent: Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, pancreatitis.

Frequency unknown: Gastritis, gastroenteritis, gastro-oesophageal reflux, constipation, malabsorption, taste perversion, increased appetite.

Hepatobiliary disorders:

Frequent: Raised liver enzymes.

Frequency unknown: Hepatitis, hepatic enzyme increase (elevated aspartate aminotransferase (AST), elevated alanine aminotransferase (ALT), elevated gamma-glutamyl transferase (GGT) and hepatic failure.

Skin and subcutaneous tissue disorders:

Frequent: Rash, pruritus, and increased sweating.

Less Frequent: Erythema multiforme, skin discolouration, Stevens-Johnson syndrome, photo-allergic dermatitis.

Frequency unknown: Acne, alopecia, eczema, folliculitis, seborrhoea, skin exfoliation, urticaria, nail disorders.

Musculoskeletal, connective tissue and bone disorders:

Frequent: Arthralgia, myalgia

Frequency unknown: Myopathy.

Reproductive system and breast disorders:

Less frequent: Gynaecomastia

Frequency unknown: Impotence, decreased libido, increased libido.

General disorders and administrative site conditions:

Frequent: Fatigue and pain.

Frequency unknown: Alcohol intolerance, allergic reaction, asthenia, hot flushes, influenza-like symptoms, malaise, pain, syncope, and redistribution/accumulation of body fat.

The following adverse reactions have been reported for Efavirenz/ Emtricitabine/ Tenofovir fixed dose combination

Infections and Infestations:

Frequent: Sinusitis, upper respiratory tract infections, nasopharyngitis.

Immune system disorders:

Frequent: Immune reconstitution syndrome.

Endocrine disorders:

Frequency unknown: Cushingoid appearance, accumulation of body fats, dorsocervical fat enlargement (buffalo hump).

Psychiatric disorders:

Frequent: Depression, insomnia, abnormal dreams.

Nervous system disorders:

Frequent: Somnolence, headache, dizziness.

Gastrointestinal disorders:

Frequent: Nausea, diarrhoea, vomiting.

Skin and subcutaneous tissue disorders:

Frequent: Rash.

General disorders and administration site conditions:

Frequency unknown: Fatigue.

Investigations:

Frequency unknown: 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.

c) Description of selected adverse reactions

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, 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.
- 28 or 30 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

23 October 2025