Professional information for medicines for human use

PRODUCT NAME: TEEVIR

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

TEEVIR film-coated tablets

Tenofovir disoproxil fumarate 300 mg, efavirenz 600 mg, emtricitabine 200 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Tenofovir disoproxil fumarate 300 mg equivalent to 245 mg tenofovir disoproxil

Efavirenz 600 mg

Emtricitabine 200 mg

Contains sugar (lactose monohydrate 120 mg per tablet).

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pink coloured, capsule shaped, film-coated tablets debossed with “M171” on one side and plain on the other side.

4. CLINICAL PARTICULARS

Approved PI- 17/02/2025

4.1 Therapeutic indications

TEEVIR is indicated for use alone as a complete regimen or in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults.

4.2 Posology and method of administration

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

Posology

Adults:

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

Method of administration:

It is recommended that TEEVIR be swallowed whole with water.

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

It is anticipated that tenofovir exposure will be approximately 35 % lower following administration of TEEVIR on an empty stomach as compared to the individual component tenofovir disoproxil fumarate when taken with food. In virologically suppressed patients, the clinical relevance of this reduction can be expected to be limited. Further data on the clinical translation of the decrease in pharmacokinetic exposure is awaited.

Children and adolescents:

TEEVIR is not recommended for use in children below 18 years of age due to lack of data on safety and efficacy.

Elderly:

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

Dose adjustment:

If TEEVIR is co-administered with rifampicin, an additional 200 mg/day (800 mg total) of efavirenz is recommended.

Renal insufficiency:

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

Hepatic impairment:

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

TEEVIR is contraindicated in patients with severe hepatic impairment.

It is important to take TEEVIR on a regular dosing schedule to avoid missing doses. Patients should be told that if they forget to take TEEVIR 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.

4.3 Contraindications

- Hypersensitivity to TEEVIR or to any of the excipients.
- TEEVIR must not be used in patients with severe hepatic impairment.

- TEEVIR must not be administered concurrently with astemizole, cisapride, midazolam, triazolam, pimozide, bepridil, or ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine), because competition for cytochrome P450 CYP3A4 by efavirenz could result in inhibition of metabolism and create the potential for serious and/or life-threatening undesirable effects (for example, cardiac dysrhythmias, prolonged sedation or respiratory depression).
- Herbal preparations containing St. John's Wort (Hypericum perforatum) must not be used while taking TEEVIR due to the risk of decreased plasma concentrations and reduced clinical effects of TEEVIR.
- Efavirenz significantly decreases voriconazole plasma concentrations while voriconazole also significantly increases efavirenz plasma concentrations. Since TEEVIR is a fixed- dose combination product, the dose of efavirenz cannot be altered; therefore, voriconazole and TEEVIR must not be co-administered.

- TEEVIR must not be used in patients with moderate to severe renal impairment (creatine clearance < 50 ml/min) (see 4.4 Special warnings and precautions for use and 4.2 Posology and method of administration).
- TEEVIR must not be used during pregnancy and breast-feeding (see 4.6 Fertility, pregnancy and lactation).
- TEEVIR must not be used in patients younger than 18 years of age due to lack of safety and efficacy.
- TEEVIR must not be used concomitantly with medicinal products containing any of the components efavirenz, emtricitabine or tenofovir, or who concomitantly take other cytidine analogues, such as lamivudine and adefovir dipivoxil.

4.4 Special warnings and precautions for use

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.

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

General:

ALERT: Find out about medicines that should NOT be taken with TEEVIR or any of the active ingredients of TEEVIR (**see 4.3 Contraindications, 4.5 Interaction with other medicinal products and other forms of interaction and 4.8 Undesirable effects**).

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

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 TEEVIR, 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 TEEVIR to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors.

Treatment with TEEVIR should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxitity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Patients with HIV and hepatitis B virus co-infection:

It is recommended that all patients with HIV be tested for the presence of hepatitis B virus (HBV) before initiating antiretroviral therapy. TEEVIR is not indicated for the treatment of chronic HBV infection and the safety and efficacy of TEEVIR have not been established in patients co-infected with HBV and HIV. Severe acute exacerbations of hepatitis B have been reported in patients after the discontinuation of emtricitabine (200 mg) and tenofovir disoproxil fumarate. Hepatic function should be closely monitored with both clinical and laboratory follow up for at least several months in patients who discontinue TEEVIR and are co-infected with HIV and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

Renal impairment:

Emtricitabine and tenofovir, two of the active ingredients in TEEVIR are principally eliminated by the

kidneys. Dosing interval adjustment of emtricitabine and tenofovir is recommended in all patients with creatinine clearance 30 – 49 ml/min. Since this is not possible with a fixed dose combination, TEEVIR should not be administered to patients with creatinine clearance < 50 ml/min or patients requiring haemodialysis (**see 4.2 Posology and method of administration**).

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

TEEVIR should be avoided with concurrent or recent use of a nephrotoxic agent. Patients at risk for, or with a history of, renal dysfunction and patients receiving concomitant nephrotoxic agents should be carefully monitored for changes in serum creatinine and phosphorous.

Lipodystrophy and metabolic abnormalities

Combination antiretroviral therapy has been associated with the redistribution/accumulation of body fat, including central obesity, dorso-cervical 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

Immune reconstitution inflammatory syndrome (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 ART 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 ART 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.

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have

been reported, particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (cART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Opportunistic infections

Patients receiving TEEVIR should be advised that they may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close observation by healthcare professionals experienced in the treatment of patients with associated HIV disease. 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 TEEVIR, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Lactic acidosis/hyperlactataemia

Use of TEEVIR can result in potentially fatal lactic acidosis as a consequence of mitochondrial dysfunction. Clinical features are non-specific, and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss. In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal < 2 mmol/ℓ) and the serum bicarbonate and respond as follows:

- Lactate 2-5 mmol/ℓ with minimum symptoms: switch to agents that are less likely to cause lactic acidosis.

- Lactate 5-10 mmol/ℓ with symptoms and/or with reduced standard bicarbonate: Stop 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.

Caution should be exercised when administering TEEVIR to patients with known risk factors for liver disease.

Treatment with TEEVIR should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

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 post-natally to nucleoside analogues. Apart from lactic acidosis/hyperlactataemia (see above) other manifestations of mitochondrial dysfunction include haematological disorders (anaemia, neutropenia), and peripheral neuropathy.

Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). It is not known whether the neurological disorders are transient or permanent. Any fetus exposed in utero to nucleoside and nucleotide analogues, even HIV negative infants/children, should

have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant sign and symptoms.

Pancreatitis

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

Patients with moderate to severe renal impairment

In patients with moderate to severe renal impairment, the terminal half-life of TEEVIR is increased due to decreased clearance. The dose of TEEVIR should therefore be adjusted (see 4.2 Posology and method of administration).

Liver disease

Use of TEEVIR can result in hepatomegaly due to nonalcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of TEEVIR 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 package inserts for these medicines.

Patients with preexisting 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.

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 package inserts for these medicines.

Patients co-infected with HIV and HBV who discontinue TEEVIR 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.

Discontinuation of TEEVIR therapy in patients coinfected with HIV and HBV may be associated with severe, acute exacerbations of hepatitis.

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

Where discontinuation of therapy with one of the components of TEEVIR is indicated or where dose modification is necessary, separate preparations of efavirenz, emtricitabine and tenofovir disoproxil fumarate are available. Please refer to the package inserts for these products.

If therapy with TEEVIR 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.

Medicine interactions

ALERT: Find out about medicines that should NOT be taken with TEEVIR (see 4.5 Interaction with other medicines and other forms of interaction).

Since emtricitabine and tenofovir are primarily eliminated by the kidneys, co-administration of TEEVIR with medicines that reduce renal function or compete for active tubular secretion may increase serum concentrations of emtricitabine, tenofovir, and/or other renally eliminated medicines. Some examples include, but are not limited to adefovir dipivoxil, cidofovir, acyclovir, valaciclovir, ganciclovir and valganciclovir.

TEEVIR should not be co-administered with emtricitabine (200 mg), tenofovir or efavirenz. Due to similarities between emtricitabine and lamivudine, TEEVIR should not be co- administered with other medicines containing lamivudine, including lamivudine and zidovudine co-formulation, lamivudine for HIV, lamivudine for HBV, abacavir sulphate and lamivudine coformulation or abacavir sulphate, lamivudine and zidovudine co-formulation.

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 – 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.

Paediatric use

Safety and efficacy in paediatric patients have not been established.

Use in the Elderly

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

Skin rash

Mild-to-moderate rash has been reported with efavirenz use and usually resolves with continued therapy. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash. TEEVIR should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. Prophylaxis with appropriate antihistamines prior to initiating therapy with TEEVIR in children may be considered.

Nervous system symptoms

Nervous system symptoms have been reported with efavirenz use (see **4.8 Undesirable effects**). 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 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 TEEVIR may be 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 TEEVIR needs to be weighed against the unknown risks of significant liver toxicity (see **4.8 Undesirable effects**).

Monitoring of cholesterol and triglycerides should be considered in patients treated with TEEVIR (see 4.8 Undesirable effects).

Lactose

TEEVIR contains lactose and should not be given to patients with rare hereditary problems,

or a history of galactose intolerance, Lapp lactose deficiency or glucose- galactose malabsorption.

4.5 Interaction with other medicines and other forms of interaction

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

TEEVIR should not be administered concomitantly with other medicinal products containing any of the components, efavirenz, emtricitabine or tenofovir disoproxil as fumarate. Due to similarities with emtricitabine, TEEVIR should not be administered concomitantly with other cytidine analogues, such as lamivudine and adefovir dipivoxil (**see 4.3 Contraindications**).

Efavirenz is an inducer of CYP3A4 and an inhibitor of some CYP450 iso-enzymes including CYP3A4. Other compounds that are substrates of CYP3A4 may have decreased plasma concentrations when co-administered with efavirenz. Efavirenz exposure may also be altered when given with medicinal products or food (for example, grapefruit juice) which affect CYP3A4 activity.

Concomitant use

TEEVIR must not be administered concurrently with astemizole, cisapride, midazolam, triazolam,

pimozide, bepridil, or ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine), since inhibition of their metabolism may lead to serious, life-threatening events (see 4.3 Contraindications).

Voriconazole

Co-administration of standard doses of efavirenz and voriconazole is contraindicated due to significant increases in the AUC and Cmax of efavirenz and significant decreases in the AUC and Cmax of voriconazole. Since TEEVIR is a fixed-dose combination product, the dose of efavirenz cannot be altered; therefore, voriconazole and TEEVIR must not be co- administered (see 4.3 Contraindications).

Renally eliminated medicinal products

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

Use of TEEVIR should be avoided with concurrent or recent use of a nephrotoxic medicinal product. Some examples include, but are not limited to, aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2.

Other interactions

Interactions between the components of TEEVIR and protease inhibitors, antiretroviral agents other than protease inhibitors and other non-antiretroviral medicinal products are summarised in the Table below.

Interactions between the individual components of TEEVIR and other medicinal products

Medicinal product by therapeutic areas	Effect (increase is indicated as "↑", decrease as "↓", no change as "↔")	Recommendation concerning coadministration with TEEVIR
ANTI-INFECTIVES		
Antiretrovirals		
Protease inhibitors		
Amprenavir/Efavirenz	AUC, Cmax and Cmin of Amprenavir ~↓ 40 %	Efavirenz has the potential to decrease serum concentrations of amprenavir, hence co-administration of amprenavir and TEEVIR is not recommended.
Atazanavir/ Ritonavir/ Tenofovir disoproxil fumarate	↓ Atazanavir plasma concentration Co-administration of atazanavir/ritonavir with tenofovir resulted in increased exposure to	Insufficient data available to make dosing recommendation for atazanavir/ritonavir when dosed with TEEVIR.

	tenofovir. Higher tenofovir plasma concentrations could potentiate tenofovir associated adverse events, including renal disorders.	Co-administration of Atazanavir/ritonavir and TEEVIR is not recommended.
Atazanavir/ Ritonavir/ Efavirenz	↓ Atazanavir plasma concentration 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.	
Indinavir/Efavirenz	— Efavirenz plasma concentration ↓ Indinavir plasma concentration While the clinical significance of decreased indinavir plasma concentrations has not been	Insufficient data available to make dosing recommendation for indinavir when dosed with TEEVIR.

	established, the magnitude of the observed pharmacokinetic interaction should be taken into consideration when choosing a regimen containing both efavirenz, a component of TEEVIR and indinavir.	
Indinavir/Emtricitabine	— Indinavir plasma concentration Emtricitabine plasma concentration	
Indinavir/Tenofovir disoproxil fumarate	— Indinavir plasma concentration ↔Tenofovir plasma concentration	
Lopinavir/ Ritonavir/ Tenofovir disoproxil fumarate	Lopinavir/Ritonavir plasma concentration ↑ Tenofovir plasma concentration Higher tenofovir plasma concentrations could potentiate tenofovir-associated adverse events, including renal disorders.	Insufficient data to make dosing recommendation for lopinavir / ritonavir when dosed with TEEVIR. Co-administration of lopinavir / ritonavir and TEEVIR not recommended.
Lopinavir/Ritonavir/ Efavirenz	Co-administration of lopinavir/ ritonavir with efavirenz resulted in substantial decrease in lopinavir exposure,	

	necessitating dosage adjustment of lopinavir/ritonavir	
Ritonavir/Efavirenz	↑ Ritonavir plasma concentration ↑ Efavirenz plasma concentration (inhibition of CYP-mediated oxidative metabolism) When efavirenz was given with ritonavir 500 mg or 600 mg twice daily, the combination was not well tolerated (for e.g., dizziness, nausea, paraesthesia and elevated livere nzymes occurred). Sufficient data on the tolerability of efavirenz with low-dose ritonavir (100 mg, once or twice daily) are not available.	Co-administration of ritonavir at doses of 600 mg and TEEVIR is not recommended. Using and TEEVIR in a regimen including low-dose ritonavir, the possibility of increase in the incidence of efavirenz-associated adverse events should be considered, due to possible pharmacodynamic interaction. Monitoring of liver enzymes is recommended when and TEEVIR is used in combination with ritonavir.
Saquinavir/Efavirenz	↓ Saquinavir plasma concentration;	Co-administration with

	CYP3A4 induction ↓ Efavirenz plasma concentration	saquinavir as the sole protease inhibitor and TEEVIR is not recommended
Saquinavir/Tenofovir disoproxil fumarate	— Saquinavir plasma concentration Tenofovir plasma concentration Co-administration of tenofovir disoproxil fumarate with ritonavir boosted saquinavir; no pharmacokinetic interaction.	
Saquinavir/ Ritonavir/ Efavirenz	No data are available on the potential interactions of efavirenz with combination of saquinavir and ritonavir. Co-administration of efavirenz with low-dose ritonavir in combination with a protease inhibitor: see ritonavir above.	Insufficient data are available to make a dosing recommendation for saquinavir/ritonavir when dosed with TEEVIR. Co-administration of saquinavir/ritonavir and TEEVIR not recommended
NRTIs and NNRTIs		
NRTIs/Efavirenz	Specific interaction studies not performed with efavirenz and NRTIs, other than lamivudine, zidovudine and tenofovir disoproxil fumarate.	Due to similarities with emtricitabine, TEEVIR should not be administered with other cytidine analogues,

	Clinically significant interaction not expected since NRTIs are metabolised via a different route than efavirenz and unlikely to compete for the same metabolic enzymes and elimination pathways.	such as lamivudine
NNRTIs/Efavirenz	Interaction not studied. Potential for pharmacokinetic or pharmacodynamic interactions is unknown.	Since use of two NNRTIs proved not beneficial in terms of efficacy and safety, co-administration of TEEVIR and another NNRTI is not recommended
Didanosine/Tenofovir disoproxil fumarate	Co-administration of tenofovir disoproxil fumarate and didanosine results in a 40-60 % increase in systemic exposure to didanosine that may increase the risk for didanosine- related adverse events. Cases of pancreatitis and lactic acidosis, sometimes fatal, have been reported. Co-administration of tenofovir disoproxil fumarate and didanosine at a	Co-administration of TEEVIR and didanosine not recommended

	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. 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.	
Antibiotics		
Clarithromycin/ Efavirenz	↓Clarithromycin plasma concentration ↑ Clarithromycin 14-hydroxymetabolite plasma concentration — Efavirenz plasma concentration (CYP3A4 induction) Rash developed in 46 % of uninfected volunteers receiving efavirenz and	Clinical significance of these changes in clarithromycin plasma levels is not known. Alternatives to clarithromycin (e.g. azithromycin) may be considered. Other macrolide antibiotics, such as erythromycin, have not been studied in combination with

	clarithromycin	TEEVIR
Antimycobacterials		
Rifabutin/Efavirenz	↓ Rifabutin concentration — Efavirenz concentration (CYP3A4 induction)	Daily dose of rifabutin should be increased by 50 % when given with TEEVIR. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week in combination with TEEVIR
Rifampicin/Efavirenz	↓ Efavirenz plasma concentration (CYP3A4 and CYP2B6 induction)	Additional 200mg/day (800mg total) of efavirenz recommended when rifampicin is co-administered with TEEVIR. No dose adjustment of rifampicin recommended when given with TEEVIR
Rifampicin/Tenofovir disoproxil fumarate	— Rifampicin plasma concentration Tenofovir plasma concentration	
Antifungals		
Itraconazole/Efavirenz	↓ Itraconazole plasma concentration	Dose recommendations cannot

	due to CYP3A4 induction — Efavirenz plasma concentration	be made for use of TEEVIR in combination with itraconazole. Alternative antifungal treatment should be considered
Voriconazole/ Efavirenz	↓ Voriconazole plasma concentration ↑ Efavirenz concentration (competitive inhibition of oxidative metabolism). Co-administration of standard doses of efavirenz and voriconazole is contraindicated	TEEVIR is a fixed-dose combination product, the dose of efavirenz cannot be altered; voriconazole and TEEVIR must not be co-administered
ANTICONVULSANTS		
Carbamazepine/ Efavirenz	↓ Carbamazepine plasma concentration due to CYP3A4 induction ↓ Efavirenz plasma concentration due to CYP3A4 and CYP2B6 induction Co-administration of higher doses of either efavirenz or carbamazepine has not been studied.	No dose recommendation can be made for the use of TEEVIR with carbamazepine. Alternative anticonvulsants should be considered. Carbamazepine plasma levels should be monitored periodically.

Phenytoin, Phenobarbital, and other anticonvulsants	Interaction not studied with efavirenz, emtricitabine or tenofovir disoproxil fumarate. There is a potential for reduction or increase in the plasma concentrations of phenytoin, phenobarbital and other anticonvulsants that are substrates of CYP450 iso-enzymes.	When TEEVIR is co-administered with an anticonvulsant that is substrate of CYP450 iso- enzymes, periodic monitoring of anticonvulsant levels to be conducted.
Vigabatrin/Efavirenz	Interaction not studied. Clinically significant interactions not expected as vigabatrin and gabapentin are exclusively eliminated unchanged in the urine and unlikely to compete for same metabolic enzymes and elimination pathways as efavirenz.	TEEVIR and vigabatrin or gabapentin can be co-administered without dose adjustment.
Gabapentin/Efavirenz		
ANTIDEPRESSANTS		

Selective Serotonin Reuptake Inhibitors (SSRIs)		
Sertraline/Efavirenz	↓Sertraline plasma concentration — Efavirenz plasma concentration (CYP3A4 induction)	When co-administered with TEEVIR sertraline dose increases should be guided by clinical response.
Paroxetine/Efavirenz	— Paroxetine plasma concentration Efavirenz plasma concentration	TEEVIR and paroxetine can be co-administered
Fluoxetine/Efavirenz	Interaction not studied. Since fluoxetine shares a similar metabolic profile with paroxetine, i.e. a strong CYP2D6 inhibitory effect, a similar lack of interaction would be expected for fluoxetine.	TEEVIR and fluoxetine can be co-administered
CARDIOVASCULAR AGENTS		
Calcium Channel Blockers		
Diltiazem/Efavirenz	↓ Diltiazem plasma concentration ↑ Efavirenz plasma concentration	Dose adjustments of diltiazem when co-administered with TEEVIR should be guided by

	(CYP3A4 induction) Increase in efavirenz pharmacokinetic parameters not considered clinically significant.	clinical response.
Verapamil, Felodipine, Nifedipine and Nicardipine	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 calcium channel blockers when co-administered with TEEVIR should be guided by clinical response.
LIPID LOWERING MEDICINAL PRODUCTS		
HMG Co-A Reductase Inhibitors		
Atorvastatin/Efavirenz	↓ Atorvastatin plasma concentration ↓ Total active HMG Co-A reductase inhibitors concentration	Cholesterol levels should be periodically monitored when atorvastatin, pravastatin or simvastatin is co-administered with TEEVIR. Co-administration of efavirenz with these statins did not affect
Pravastatin/Efavirenz	↓ Pravastatin plasma concentration	
Simvastatin/Efavirenz	↓ Simvastatin plasma concentration	

	↓ Total HMG Co-A reductase inhibitors concentration (CYP3A4 induction)	efavirenz pharmacokinetic values, although dose adjustment of the statins may be required.
HORMONAL CONTRACEPTIVES		
Ethinyl oestradiol/Efavirenz	↑ Ethinyl oestradiol plasma concentration — Efavirenz plasma concentration Clinical significance of the effect on ethinyl oestradiol AUC is not known.	Because the potential interaction of efavirenz, a component of TEEVIR, in combination with oral contraceptives has not been fully characterised, a reliable method of barrier contraception must be used in addition to oral contraceptives.
Ethinyl oestradiol/ Tenofovir disoproxil fumarate	- Ethinyl oestradiol plasma concentration Tenofovir plasma concentration	
OPIOIDS		
Methadone/Efavirenz	↓ Methadone plasma concentration(CYP3A4 induction) In a study of HIV infected intravenous medicine users, coadministration of efavirenz with methadone resulted in	Patients receiving methadone and TEEVIR concomitantly should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms

	decreased plasma levels of methadone and signs of opiate withdrawal. Methadone dose was increased by a mean of 22 % to alleviate withdrawal symptoms.	
Methadone/Tenofovir disoproxil fumarate	— Methadone plasma concentration Tenofovir plasma concentration	
HERBAL PRODUCTS		
St. John's Wort (*Hypericum perforatum*) / Efavirenz	↓ Efavirenz plasma concentration by concomitant use of St. John's Wort due to induction of medicine metabolising enzymes and/or transport proteins by St. John's Wort. This may result in loss of therapeutic effect and development of resistance (See **4.3 Contraindications**)	Co-administration of TEEVIR and St. John's Wort is contraindicated. If a patient is taking St. John's Wort, discontinue use of St. John's Wort and check viral levels and efavirenz levels. Efavirenz levels may increase on discontinuing St. John's Wort. The inducing effect of St. John's Wort may persist for at least 2

		weeks after cessation of treatment.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established.

There are no adequate or well-controlled studies of TEEVIR or its components in pregnant women.

A small number of cases of neural tube defects, including meningomyelocele, have been reported but causality has not been established. Studies of efavirenz in animals have shown reproductive toxicity including marked teratogenic effects.

TEEVIR should not be used during pregnancy.

Women of childbearing potential

Pregnancy should be avoided in women receiving TEEVIR. Barrier contraception should always be used in combination with other methods of contraception (for example, oral or other hormonal contraceptives) while on therapy with TEEVIR. Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of TEEVIR is recommended. Women of childbearing potential should undergo pregnancy testing before initiation of TEEVIR.

Lactation

Studies in rats have demonstrated that efavirenz and tenofovir are excreted in milk; concentrations of efavirenz were much higher than those in maternal plasma. It is not known whether efavirenz, emtricitabine or tenofovir are excreted in human milk. Because of the potential for both HIV transmission and the potential for serious undesirable effects in breastfeeding infants, mothers should be instructed not to breast-feed if they are receiving TEEVIR.

4.7 Effects on ability to drive and use machines

Efavirenz, and therefore TEEVIR, 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

Side-effects

EMTRICITABINE

Blood and lymphatic system disorders

Frequencies unknown: Neutropenia, anaemia

Metabolism and nutrition disorders

Frequencies unknown: Lactic acidosis, usually associated with severe hepatomegaly and steatosis, has been associated with nucleoside reverse transcriptase inhibitors. Hypertriglyceridaemia and hyperglycaemia.

Nervous system disorders

Frequent: Headache, asthenia

Less frequent: Neuritis, paraesthesia and peripheral neuropathy and dizziness

Psychiatric disorders

Less frequent: Depressive disorders, sleep disturbances, abnormal dreams, insomnia

Respiratory, thoracic and mediastinal disorders

Frequent: Increased cough, rhinitis

Gastrointestinal disorders

Frequent: Nausea, diarrhoea

Less frequent: Abdominal pain, dyspepsia and vomiting

Hepatobiliary disorders

Frequencies unknown: Raised liver enzyme concentrations and hyperbilirubinaemia

Skin and subcutaneous tissue disorders

Less frequent: Skin rashes (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.

Musculoskeletal system disorders

Less frequent: Arthralgia, myalgia

Renal and urinary system disorders

Frequent: Elevation of creatinine

TENOFOVIR

Blood and lymphatic system disorders

Frequencies unknown: Neutropenia, haematuria

Immune system disorders

Frequencies unknown: Allergic reactions

Metabolism and nutrition disorders

Frequencies unknown: Lactic acidosis, usually associated with severe hepatomegaly and steatosis; also hypertriglyceridaemia, hyperglycaemia, hyperphosphataemia

Nervous system disorders

Frequent: Asthenia

Less frequent: Anorexia

Frequencies unknown: Headache, dizziness and peripheral neuropathy

Psychiatric disorders

Frequencies unknown: Depression, insomnia and anxiety

Respiratory, thoracic and mediastinal disorders

Frequencies unknown: Chest pain, pneumonia, dyspnoea

Gastrointestinal disorders

Frequent: Nausea, vomiting, diarrhoea

Less frequent: Raised serum amylase concentrations, abdominal pain and flatulence

Frequencies unknown: Pancreatitis and dyspepsia

Hepatobiliary disorders

Less frequent: Hepatotoxicity, including lactic acidosis

Frequencies unknown: Raised liver enzymes and hepatitis

Skin and subcutaneous tissue disorders

Frequencies unknown: Skin rashes (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash and pustular rash)

Musculoskeletal system disorders

Frequent: decrease in bone mineral density

Frequencies unknown: Back pain, myalgia, arthralgia

Renal and urinary system disorders

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

General disorders and administrative site conditions

Frequencies unknown: Fever, sweating and weight loss

EFAVIRENZ

Metabolism and nutritional system disorders

Frequencies unknown: Weight gain and weight loss

Nervous system disorders

Frequent: Dizziness, impaired concentration, somnolence and headache

Less frequent: Anorexia and hypoaesthesia

Frequencies unknown: Abnormal co-ordination, ataxia, convulsions, paraesthesia, neuropathy, tremors, amnesia, increased appetite, confusion, impaired co-ordination, impotence, decreased libido, increased libido, neuralgia, peripheral neuropathy, speech disorder and vertigo

Psychiatric disorders

Frequent: Insomnia

Less frequent: Abnormal dreams

Frequencies unknown: Aggravated depression, agitation, anxiety, apathy, confusion, emotional lability, euphoria and hallucination

Eye disorders

Frequencies unknown: Abnormal vision

Ear and labyrinth disorders

Frequencies unknown: Tinnitus

Cardiac disorders

Frequencies unknown: Flushing

Vascular disorders

Frequencies unknown: Palpitations and tachycardia

Respiratory system disorders

Frequencies unknown: Asthma, sinusitis, dyspnoea and upper respiratory tract infections

Gastrointestinal disorders

Frequent: Nausea, vomiting and diarrhoea

Less frequent: Dyspepsia and abdominal pain

Frequencies unknown: Gastritis, gastro-enteritis, gastro-oesophageal reflux, constipation and malabsorption, taste perversion

Hepatobiliary disorders

Frequencies unknown: Hepatitis, hepatic enzyme increase and hepatic failure

Skin and subcutaneous tissue disorders

Frequent: Rash, pruritus and increased sweating

Frequencies unknown: Acne, alopecia, eczema, folliculitis, seborrhea, skin exfoliation, urticaria, erythema multiforme, nail disorders, skin discolouration, Stevens-Johnson syndrome

Musculoskeletal system disorders

Frequencies unknown: Arthralgia, myalgia and myopathy

General disorders and administrative site conditions

Frequent: Fatigue and pain

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

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 4.4 Special warnings and precautions for use).

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 + STC 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 toxicity (see 4.4 Special warnings and precautions for use).

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 asked to

report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form” found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

If overdose occurs the patient must be monitored for evidence of toxicity and standard supportive treatment supplied as necessary.

Emtricitabine

Limited clinical experience is available at doses higher than the therapeutic dose of emtricitabine (200 mg).

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. 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 four-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

Mechanism of action:

Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1). Efavirenz non-competitively inhibits HIV-1 reverse transcriptase (RT) and does not significantly inhibit human immunodeficiency virus-2 (HIV-
2) RT or cellular deoxyribonucleic acid (DNA) polymerases (α, β, γ, and δ). Emtricitabine is a nucleoside analogue of cytidine. Tenofovir disoproxil fumarate is converted in vivo to tenofovir, a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate.

Emtricitabine and tenofovir are nucleoside reverse transcriptase inhibitors (NRTI's) and are phosphorylated by cellular enzymes to form emtricitabine triphosphate and tenofovir diphosphate, respectively. In vitro studies have shown that both emtricitabine and tenofovir can be phosphorylated when combined together in cells. Emtricitabine triphosphate and tenofovir diphosphate competitively

inhibit HIV-1 reverse transcriptase, resulting in DNA chain termination.

Both emtricitabine triphosphate and tenofovir diphosphate are weak inhibitors of mammalian DNA polymerases.

Antiviral activity in vitro:

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

Resistance:

Resistance to efavirenz can be selected in vitro and resulted in single or multiple amino acid substitutions in HIV-1 RT, including L100I, V108I, V179D, and Y181C. K103N was the most frequently observed RT substitution in viral isolates from patients who experienced rebound in viral load during clinical studies of efavirenz. Substitutions at RT positions 98, 100, 101, 108, 138, 188, 190 or 225 were also observed, but at lower frequencies, and often only in combination with K103N. Cross-resistance profiles for efavirenz, nevirapine and delavirdine in vitro demonstrated that the K103N substitution confers loss of susceptibility to all three NNRTIs.

Resistance to emtricitabine or tenofovir has been seen in vitro and in some HIV-1 infected patients due to the development of an M184V or M184I substitution in RT with emtricitabine or a K65R substitution in RT with tenofovir. Emtricitabine-resistant viruses with the M184V/I mutation were cross-resistant to lamivudine, but retained sensitivity to didanosine, stavudine, tenofovir and zidovudine. The

K65R mutation can also be selected by abacavir or didanosine and results in reduced susceptibility to these agents plus lamivudine, emtricitabine and tenofovir. Tenofovir disoproxil fumarate should be avoided in patients with HIV-1 harbouring the K65R mutation. Both the K65R and M184V/I mutation remain fully susceptible to efavirenz.

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

Resistance analysis was performed on plasma HIV-1 isolates from patients with confirmed HIV RNA > 400 copies/ml at week 144 or early study medicine discontinuation where efavirenz, emtricitabine and tenofovir disoproxil fumarate were used as individual formulations in antiretroviral treatment-naïve patients.

Genotypic resistance to efavirenz, predominantly the K103N mutation, occurred most frequently.

The M184V/I mutation was observed in (10,5 %) analysed patient isolates in the efavirenz/emtricitabine/tenofovir disoproxil fumarate group and in (34,5 %) analysed patient isolates in the group that received efavirenz and a fixed combination of lamivudine and zidovudine (p-value = 0,021). No patient in either treatment group developed the K65R mutation and no patient in the efavirenz/emtricitabine/tenofovir disoproxil fumarate group developed novel mutations associated with phenotypic resistance to either emtricitabine or tenofovir.

5.2 Pharmacokinetic properties

Absorption, distribution, metabolism, and excretion:

Adults:

Emtricitabine:

Following oral administration of emtricitabine (200 mg), emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1 – 2 hours post-dose. In vitro binding of emtricitabine to human plasma proteins is < 4 % and is independent of concentration over the range of 0,022 – 200 µg/ml. Median (range) fasted oral bioavailability of emtricitabine is 92 % (83,1 – 106,4 %). Mean (± SD) Cmax (maximum plasma concentrations) 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 radiolabeled 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 secretion with a renal clearance in adults with normal renal function of 213 ± 89 ml/min (mean ± SD). 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 a single 300 mg dose of tenofovir DF to HIV-infected patients in the fasted state, maximum serum concentrations (Cmax) were achieved in 1,0 ± 0,4 hours, mean (± SD)

Cmax.and AUC values were 296 – 90 ng/ml and 2,287 ± 685 ng.hr/ml, respectively. Median (range) fasted oral bioavailability of tenofovir is 25 % (NC – 45 %). In vitro binding of tenofovir to human plasma proteins is < 0,7 % and is independent of concentration over the range of 0,01 – 25 µg/ml.

Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion with a renal clearance in adults with normal renal function of 243 ± 33 ml/min (mean ± SD). 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 – 5 hours and steady state plasma concentrations are reached in 6 – 10 days.

Efavirenz is highly bound (approximately 99,5 – 99,75 %) to human plasma proteins, predominantly albumin.

Following administration of 14C-labelled efavirenz, approximately 14 – 34 % of a radio- labelled dose of efavirenz was recovered in the urine (mostly as metabolites) and 16 – 61
% was recovered in faeces (mostly as parent medicine). 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 the induction of its own metabolism.

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

Effect of food:

The fixed-dose combination TEEVIR has not been evaluated in the presence of food.

Administration of efavirenz capsules with a high fat meal increased the mean AUC and Cmax of efavirenz by 28 % and 79 %, respectively, compared to administration in a fasted state. Compared to fasted administration, dosing of tenofovir disoproxil fumarate and emtricitabine in combination with either a high fat meal or a light meal increased the mean AUC and Cmax of tenofovir by 35 % and 15 %, respectively without affecting emtricitabine exposures.

Special populations

Paediatric and elderly patients:

Pharmacokinetic studies of tenofovir DF have not been performed in paediatric patients (less than 18 years). Efavirenz has not been studied in paediatric patients below 3 years of age or who weighs less than 13 kg. Emtricitabine has been studied in paediatric patients from 3 months to 17 years of age. TEEVIR is not recommended for paediatric administration. Pharmacokinetics of efavirenz, emtricitabine and tenofovir have not been fully evaluated in the elderly (more than 65 years).

Patients with impaired renal function:

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 impart of renal impairment on efavirenz elimination should be minimal.

Emtricitabine and tenofovir disoproxil fumarate:

The pharmacokinetics of emtricitabine and tenofovir are altered in patients with renal impairment. In patients with creatinine clearance < 50 ml/min, Cmax and AUC o-α of emtricitabine and tenofovir were increased.

Patients with impaired hepatic impairment:

Efavirenz:

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

Emtricitabine:

The pharmacokinetics of emtricitabine have not been studied in patients with hepatic impairment; however, emtricitabine is not significantly metabolised by liver enzymes, so the impact of liver impairment should be minimal.

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.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies of efavirenz in animals have shown reproductive toxicity including marked teratogenic effects.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

croscarmellose sodium

hydroxypropyl cellulose (Klucel - LF)

lactose monohydrate

magnesium stearate

microcrystalline cellulose

sodium lauryl sulfate

Film coating

black iron oxide

iron oxide red

polyethylene glycol

polyvinyl alcohol

talc

titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Shelf life 4 years.

6.4 Special precautions for storage

Store at or below 30°C. Store in the original container. Do not remove from the carton until required for use. Keep the bottle tightly closed.

6.5 Nature and contents of container

TEEVIR is packed in high density polypropylene (HDPE) bottle pack comprising of white opaque wide mouth HDPE bottle with a white opaque polypropylene (PP) screw closure with desiccant sachet or desiccant canister, packed in an outer carton in 28's/30's and 84's/90's.

TEEVIR is packed in high density polypropylene (HDPE) bottle pack comprising of blue opaque wide mouth HDPE bottle with a blue opaque polypropylene screw closure with desiccant sachet or desiccant canister, packed in an outer carton in 28's/30's and 84's/90's.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

INNOVATA PHARMACEUTICALS (PTY) LTD CROWNWOOD OFFICE PARK, BLOCK D, GROUND FLOOR 100 NORTHERN PARKWAY, ORMONDE

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8 REGISTRATION NUMBER

TEEVIR: 51/20.2.8/0579

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION TEEVIR –

02 April 2020

10 DATE OF REVISION OF THE TEXT TEEVIR –

17/02/2025