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

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 efavirenz, emtricitabine, tenofovir disoproxil fumarate or to any of the components listed in section 6.1.
- A history of previous liver injury/failure with efavirenz containing antiretroviral treatment (ART).
- Pregnancy and lactation (see section 4.6).
- Patients with moderate to severe renal impairment i.e. creatinine clearance of less than 50 ml/min (see section 4.4 and 5.2).
- TEEVIR should not be used concurrently with the following medicinal products due to CYP3A4 competition: terfenadine, astemizole, bepridil, cisapride, ergot derivatives, midazolam, pimozide or triazolam. Failure to observe this contraindication can result in reduced metabolism of these medicines and may result in serious and/or life-threatening side effects such as cardiac dysrhythmias, prolonged sedation and/or respiratory depression (see section 4.5).
- TEEVIR and voriconazole should not be administered concurrently because voriconazole plasma concentrations are reduced significantly by efavirenz (see section 4.5).
- TEEVIR should not be co-administered with herbal preparations containing St. John's wort (Hypericum perforatum) due to the risk of decreased plasma concentrations and reduced clinical effects of efavirenz (see sections 4.4 and

4.5).

- Administration to patients 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. - a history of symptomatic cardiac dysrhythmia or with clinically relevant bradycardia or with congestive cardiac failure accompanied by reduced left ventricle ejection fraction. - severe disturbances of electrolyte balance e.g. hypokalemia or hypomagnesemia.
- Co-administration with medicinal products that are known to prolong the QTc interval (proarrhythmic). These medicinal products include: antiarrhythmics of classes IA and III, neuroleptics, antidepressants, certain antibiotics including some from the following classes: macrolides, fluoroquinolones, imidazole and triazole antifungals, certain non-sedating antihistamines (terfenadine, astemizole), cisapride, flecainide, certain antimalarials and methadone (see sections 4.4 and 4.5).

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.

Lactic acidosis/severe hepatomegaly with steatosis

Lactic acidosis and severe hepatomegaly with steatosis have been reported, including fatal cases, with the use of nucleoside analogues alone or in combination with other anti-retrovirals, with the majority being in women. Obesity and prolonged nucleoside exposure are potential 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 – 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 nucleoside/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 TEEVIR treatment.

Liver disease

Use of TEEVIR can result in hepatomegaly due to non-alcoholic 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 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.

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

Liver failure

There is some evidence that efavirenz is associated with three clinical pathological patterns of drug induced liver failure in HIV positive patients of which the sub massive necrosis histological pattern seems to be associated with 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 cell/µl and female gender.

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

Liver enzymes

In patients with a known or suspected history of Hepatitis B or C infection and in patients treated with other medications associated with liver toxicity, monitoring of liver enzymes is recommended. Caution should be exercised and the risk weighed against the benefits of therapy for patients fitting the above profile as well as those with hepatic impairment.

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

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

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 Professional Information 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 co-infected with HIV and HBV may be associated with severe, acute exacerbations of hepatitis.

Renal impairment (see section 4.3)

Efavirenz is not predominantly excreted by the kidneys while tenofovir disoproxil fumarate and emtricitabine are excreted by the kidneys. Since TEEVIR is a fixed-dose combination product and the dose of the individual components cannot be altered, patients with creatinine clearance less than 50 ml/min should not receive TEEVIR.

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

Renal impairment has been reported in association with the use of tenofovir disoproxil fumarate (see section 4.8).

It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with TEEVIR. Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment. TEEVIR should be avoided with concurrent or recent use of a nephrotoxic agent.

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 section 4.2).

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 TEEVIR is contraindicated (see section 4.3).

Psychiatric symptoms

There have been reports of patients treated with efavirenz, which is a component of TEEVIR, 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 adverse psychiatric experiences should seek medical evaluation for an assessment on whether their symptoms are related to the use of efavirenz, and thus TEEVIR (see section 4.8).

Nervous system symptoms

Nervous system symptoms that may be reported during treatment with TEEVIR are related to efavirenz, which has the potential to cause: dizziness, insomnia, impaired concentration, somnolence, abnormal dreams, hallucinations, euphoria, confusion, agitation, amnesia, stupor, abnormal thinking and depersonalisation. Nervous system symptoms are more likely to abate after the first 2 to 4 weeks of therapy. It is important to inform patients that they can expect an improvement with continued therapy and that dosing at bedtime may improve the tolerability of nervous system symptoms. Co-administration of TEEVIR with alcohol or psychoactive medicines can result in additive central nervous system effects.

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 providers experienced in the treatment of patients with associated HIV disease. Regular monitoring of viral load and CD4 counts need 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.

Triple nucleoside therapy

There have been reports of a high rate of virological failure and of emergence of resistance at an early stage when tenofovir disoproxil fumarate as in TEEVIR, was combined with lamivudine and abacavir as well as with lamivudine and didanosine as a once daily regimen.

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-natal to nucleoside analogues. Apart from lactic acidosis/hyperlactataemia (see above) other manifestations of mitochondrial dysfunction include haematological disorders (anaemia, neutropenia) and peripheral neuropathy. Some lateonset neurological disorders have been reported. It is not known whether the neurological disorders are transient or permanent. Any foetus 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 signs 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.

Skin rash

Rashes may occur and are usually mild to moderate maculopapular skin eruptions that occur within the first two weeks of initiating efavirenz therapy. In most cases the rash resolves after one month of continuing efavirenz therapy. If treatment is interrupted due to the rash, it may be re-initiated later. The various skin rashes may be treated with antihistamines and/or corticosteroids if indicated. This may result in faster resolution and improved tolerability of the rash.

TEEVIR should be discontinued in patients experiencing the following skin rashes: rashes associated with blistering, desquamation, mucosal involvement, or rashes associated with fever.

Bone effects

The effects of when tenofovir disoproxil fumarate associated changes in bone mineral density and biochemical markers on long-term bone health and future fracture risk, are not known. Osteomalacia associated with the use of tenofovir has been reported associated with proximal renal tubulopathy (see section 4.8). HIV patients who have a history of pathologic bone fracture or are at risk for osteopenia should be considered for bone monitoring. Supplementation with Vitamin D and calcium may be beneficial. If bone abnormalities are suspected, then appropriate consultation must be sought.

Bone mineral density

Decreases in bone mineral density of spine and changes in bone biomarkers from baseline are significantly greater with tenofovir disoproxil fumarate as contained in TEEVIR. Decreases in bone mineral density of the hip are significantly greater. Clinically relevant bone fractures are reported. If bone abnormalities are suspected, then appropriate consultation should be obtained. Bone monitoring should be considered for

HIV infected patients who have a history of pathologic bone fracture or are at risk of osteopenia. TEEVIR may cause a reduction in bone mineral density. The effects of tenofovir disoproxil fumarate-associated changes in bone mineral density on long-term bone health and future fracture risk are currently 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.
Bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy.

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.

Convulsions

Patients with a history of convulsions must be monitored for possible convulsions when using efavirenz therapy. Please see section 4.5 for anticonvulsants such as phenytoin and phenobarbital, for the precautions and plasma level monitoring that may be required.

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

Paediatric use

Tenofovir disoproxil fumarate has not been adequately investigated for use in paediatric patients and therefore TEEVIR is not recommended for use in patients under the age of 18 years.

Use in the elderly

In general, elderly patients should be treated cautiously, with heightened awareness that this population group tends to experience decreased hepatic, renal or cardiac function and that they usually have concomitant disease or other medicine therapy. There are insufficient studies on the use of efavirenz, emtricitabine and tenofovir by subjects 65 years and older to determine whether they do respond differently than younger subjects.

Co-administration with related medicines

Do not co-administer TEEVIR with the following related medicines:

- emtricitabine, tenofovir disoproxil fumarate, emtricitabine/tenofovir disoproxil fumarate and efavirenz.
- lamivudine, which is similar to emtricitabine including lamivudine/zidovudine, abacavir sulphate/lamivudine or abacavir sulphate/lamivudine/zidovudine.

Medicine interactions (see section 4.5)

TEEVIR is not recommended for use with products containing St. John's wort (Hypericum perforatum). Co-administration of non-nucleoside reverse transcriptase inhibitors (NNRTIs), including efavirenz, with St. John’s wort is expected to substantially decrease NNRTI concentrations and this may result in suboptimal levels of efavirenz and lead to loss of virologic response and cause possible resistance to efavirenz or to the class of NNRTIs.

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.

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

Efavirenz

Efavirenz is contraindicated for use with medicines that are eliminated predominantly by CYP3A4 hepatic enzymes and that rely on this isoenzyme for clearance (see section 4.3). Altered plasma concentrations may result after co-administration of efavirenz with medicines that are metabolised by isoenzymes 2C9, 2C19, and 3A4 (which are reportedly inhibited by efavirenz) and CYP3A4 (which is reportedly induced by efavirenz). Appropriate dose adjustments may be necessary. Inducers of the CYP3A4 isoenzyme can be expected to increase elimination of efavirenz resulting in lowered plasma concentrations. Medicines regarded as inducers of CYP3A4 include phenobarbital, rifampicin and rifabutin.

Emtricitabine and tenofovir disoproxil fumarate

Medicines such as acyclovir, adefovir, dipivoxil, cidofovir, ganciclovir, valacyclovir and valganciclovir may cause an increase in serum concentrations of emtricitabine and tenofovir. Emtricitabine and tenofovir are primarily eliminated by the kidneys, and therefore have the potential to interact with medicines that reduce renal function or compete for active tubular secretion.

Caution should be exercised when TEEVIR is given with medicines with potential for this interaction since the serum concentrations of each medicine may increase.

Tenofovir increases the plasma concentrations of didanosine. Suppression of CD4 cell counts have been observed in patients on a combination regimen of tenofovir disoproxil fumarate with didanosine at a daily dose of 400 mg. Patients receiving tenofovir disoproxil fumarate and didanosine should be monitored closely for didanosine-associated adverse events. This combination should be undertaken with caution. Didanosine should be discontinued in patients who develop didanosine-associated adverse events (Table 2 in section 4.5 can be consulted for didanosine dosing adjustment recommendations).

Although the mechanism of interaction is not clearly understood, atazanavir and lopinavir/ritonavir have been shown to increase tenofovir concentrations.

The impact of raised tenofovir serum concentrations may involve a higher incidence of tenofovirrelated adverse events including renal disorders. TEEVIR should be discontinued immediately in patients that experience tenofovir-related side effects. Table 2 in section 4.5 can be consulted for atazanavir dosing adjustment recommendations.

Important medicine interactions for TEEVIR are summarised in this leaflet and further tabulated in Table 1, based upon investigations of interaction profiles for the individual active ingredients efavirenz, emtricitabine and tenofovir disoproxil fumarate. Please also see section 4.3. Interaction studies for TEEVIR have not been conducted and therefore the information herein is not all inclusive but

highlights potentially significant interactions.

Table 1: Contraindicated medicines or medicines not recommended for use with TEEVIR

Medicine name	**Clinical comment**
Antifungal: Voriconazole	Co-administration is contraindicated as efavirenz decreases voriconazole plasma concentrations and therapeutic efficacy, whereas voriconazole increases efavirenz plasma concentrations and thereby increasing the risk of efavirenz-related side effects.
Antihistamine: Astemizole	Contraindicated as life-threatening adverse events like cardiac dysrhythmias may occur.
Ergot derivatives: Dihydroergotamine Ergonovine Ergotamine Methylergonovine	Contraindicated as life-threatening adverse events like acute ergot toxicity characterised by peripheral vasospasm and extreme ischaemia may occur.
Anti-retrovirals: Efavirenz Emtricitabine Tenofovir disoproxil fumarate Lamivudine	Use is not recommended as emtricitabine, tenofovir disoproxil fumarate, emtricitabine-tenofovir disoproxil fumarate and efavirenz are already active ingredients in TEEVIR. Lamivudine is similar to emtricitabine.
Benzodiazepines: Midazolam Triazolam	Contraindicated as life-threatening adverse events such as prolonged or increased sedation or respiratory depression

	may occur.
Calcium channel blockers: Bepridil	Contraindicated as life-threatening adverse events like cardiac dysrhythmias may occur.
Gastrointestinal motility agent: Cisapride	Contraindicated as life-threatening adverse events like cardiac dysrhythmias may occur.
Neuroleptic: Pimozide	Contraindicated as life-threatening adverse events like cardiac dysrhythmias may occur.
St. John's wort (Hypericum parforatum)	Co-administration is not recommended as efavirenz plasma concentrations may be lowered significantly.

Table 2: Medicines with established interactions and dose recommendations due to known or predicted interactions

Concomitant Medicine Class: Medicine name	**Effect**	**Clinical comment**
Antiretroviral agents:		
Protease inhibitors		
Amprenavir	↓ amprenavir concentration	Efavirenz may decrease serum concentrations of amprenavir.
Fosamprenavir calcium	↓ amprenavir concentration	Fosamprenavir (unboosted): Appropriate doses of fosamprenavir and TEEVIR with

		respect to safety and efficacy have not been established. An additional 100 mg/day (300 mg total of ritonavir) is recommended when TEEVIR is administered with fosamprenavir/ritonavir once daily. No change in the ritonavir dose is required when TEEVIR is administered with fosamprenavir plus ritonavir twice daily.
Atazanavir	↓ atazanavir concentration ↑ tenofovir concentration	Atazanavir concentrations are decreased by both Tenofovir disoproxil fumarate and efavirenz. Therefore, co-administration of TEEVIR and atazanavir is not recommended due to concerns regarding decreased atazanavir concentrations.
Indinavir	↓ indinavir concentration	The optimal dose of indinavir when given in combination with efavirenz is not known. Increasing the dose to 1 000 mg/8 hours does not compensate for the increased indinavir metabolism due to efavirenz.
Lopinavir/ritonav	↓ lopinavir	A dose increase of lopinavir/ritonavir to

ir	concentration ↑ tenofovir concentration	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). If patient monitoring reveals an increased incidence of tenofovir-related side effects TEEVIR should be discontinued.
Ritonavir	↑ efavirenz and ritonavir concentrations	The combination of ritonavir 500 mg every 12 hours and efavirenz 600 mg once daily, is associated with a higher frequency of adverse clinical experiences (e.g. dizziness, nausea, paraesthesia) and laboratory abnormalities (elevated liver enzymes). Monitoring of liver enzymes is recommended when TEEVIR is used in combination with ritonavir.
Saquinavir	↓ saquinavir concentration	If co-administered with TEEVIR, saquinavir should not be used as the sole protease inhibitor.
NRTI's		

Didanosine	↑ didanosine concentration	Didanosine-associated side effects such as pancreatitis and neuropathy may result from higher concentrations of didanosine. There is insufficient data to guide dose-adjustment in adult patients weighing less than 60 kg but for those over 60 kg the dose of didanosine must be decreased to 250 mg if co-administered with TEEVIR. Caution must be exercised if co-administration is desired and patients must be monitored closely for didanosine-related side effects. More information will appear on the didanosine professional information. When co-administered, efavirenz and didanosine may be taken under fasted conditions or with a light meal (less than 400 kcal, 20 % fat). Co-administration of TEEVIR and a buffered didanosine formulation should be under fasting conditions
Anticoagulant:		
Warfarin	↑ or ↓ warfarin	Monitor anti-coagulation levels (INR) as

	concentration	efavirenz has the potential to alter coagulation times.
Anticonvulsants		
Carbamazepine	↓carbamazepine concentration	Alternative anticonvulsant treatment should be selected as the data is insufficient to guide dosing adjustment.
Phenytoin Phenobarbital	↓ anticonvulsant concentration and ↓ efavirenz concentration	Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.
Antidepressants		
Sertraline	↓ sertraline concentrations	Clinical responses must guide an increase in the sertraline dose.
Antifungals		
Itraconazole	↓ itraconazole concentration ↓ hydroxyitraconazole concentration	Consider alternative antifungal treatment because clinical dose recommendations are unknown
Ketoconazole	↓ ketoconazole concentration	The effects of ketoconazole and TEEVIR are unknown. Efavirenz may decrease plasma concentrations of ketoconazole.
Anti-infective		

Clarithromycin	↓ clarithromycin concentration ↑ 14-OH metabolite concentration	No dose adjustment is needed for TEEVIR when used with clarithromycin. Azithromycin should be considered as an alternative to clarithromycin. Erythromycin and other macrolides have not been studied.
Antimycobacterials		
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
Rifampicin	↓ efavirenz concentration	Dosing recommendations for concomitant use of TEEVIR and rifampicin have not been established. Clinical significance of reduced efavirenz concentration is unknown.
Calcium channel blockers		
Diltiazem Others (e.g.	↓ diltiazem concentration ↓ desacetyl diltiazem concentration	Diltiazem dose adjustments should be undertaken in consultation with the diltiazem professional information, TEEVIR dose need not be adjusted. The potential exists for reduction in plasma

felodipine, nicardipine, nefedipine, verapamil)	↓ N-monodesmethyl diltiazem concentration ↓ calcium channel blocker concentration	concentrations of the calcium channel blocker. Dose adjustments should be guided by clinical response in consultation with the complete professional information for the calcium channel blocker.
HMG-CoA reductase inhibitors		
Atorvastatin Pravastatin Simvastatin	↓ atorvastatin, pravastatin and simvastatin concentrations	The concentrations of the HMG-CoA reductase inhibitors are decreased by efavirenz and dose adjustments may be done with reference to the individual product professional information.
Narcotic analgesics		
Methadone	↓ methadone concentrations	Co-administration of efavirenz in HIV-infected individuals with a history of injection medicine use caused a decrease in methadone plasma levels and signs of opiate withdrawal. Close patient monitoring and dose adjustment to increase methadone upon appearance of withdrawal symptoms until alleviation of

		symptoms is recommended. Concomitant administration with TEEVIR is contraindicated due to the risk for QTc prolongation (see sections 4.3 and 4.4).
Oral contraceptives		
Ethinyloestradiol	↑ ethinyloestradiol concentration	As the potential interaction with efavirenz with oral contraceptives has not been studied, a reliable barrier contraceptive must be used in addition to oral contraceptives.

Efavirenz assay interference

Interference with cannabinoid tests False positive urine cannabinoid test results have been observed in non-HIV-infected volunteers receiving efavirenz when the Microgenics Cedia DAU Multi-Level THC assay was used for screening, even though efavirenz does not bind to cannabinoid receptors. More specific confirmatory testing was performed with gas chromatography/ mass spectrometry to reveal and confirm negative results. For more information, please consult the professional information for efavirenz.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing age who are using TEEVIR should avoid falling pregnant and should ensure this by using a barrier method of contraception in combination with other methods of contraception. Pregnancy testing should also be conducted prior to initiating TEEVIR treatment.

Contraception in males and females

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

Pregnancy

TEEVIR should not be used during pregnancy.

Administration of efavirenz in the first trimester has the potential to cause harm to the unborn foetus and should the woman become pregnant, she should be educated on the potential harm to the foetus.

Efavirenz has been associated with teratogenicity in animals. Retrospective studies of pregnancies with first-trimester exposure to efavirenz as part of a combination regimen have noted a few cases of neural tube defects, including meningomyelocele.

Breastfeeding

TEEVIR should not be taken by breast-feeding women. Mothers should be instructed that they may not breastfeed their infants if they are on TEEVIR in order to avoid transmission of HIV to the infant.

Efavirenz, emtricitabine and tenofovir have been shown to be excreted in human milk. There is insufficient information on the effects of efavirenz, emtricitabine and tenofovir in newborns/infants. A risk to the infants cannot be excluded.

Fertility

No human data on the effect of TEEVIR are available. Animal studies do not indicate harmful effects of efavirenz, emtricitabine or tenofovir disoproxil on fertility.

4.7 Effects on ability to drive and use machines

Co-administration of TEEVIR with alcohol or psychoactive medicines can result in additive central nervous system effects. Patients experiencing central nervous system symptoms such as dizziness, impaired concentration and/or drowsiness should avoid tasks related to operation of machinery and other potentially hazardous tasks.

4.8 Undesirable effects

The Professional Information for efavirenz, emtricitabine and tenofovir disoproxil fumarate in combination with other anti-retroviral medicines, can be referred to for additional information TEEVIR side effects are summarised in the tables below.

Table 3: Side effects associated with the use of TEEVIR active ingredients

System Organ Class	Side effects observed with efavirenz	Side effects observed with emtricitabine and tenofovir	Efavirenz, emtricitabine and Tenofovir in combination: The following side effects

			have been reported to occur
Infections and infestations			Frequent: Sinusitis, upper respiratory tract infections, nasopharyngitis
Blood and lymphatic system disorders		Frequency unknown: Neutropenia, anaemia	
Immune system disorders			Frequent: Immune reconstitution syndrome
Endocrine disorders		Frequency unknown: Sweating, nephrogenic diabetes insipidus	Frequency unknown: Cushingoid appearance, accumulation of body fat, dorsocervical fat enlargement (buffalo hump)
Metabolism and nutrition disorders	Frequency unknown: Anorexia	Frequent: Anorexia, lactic acidosis	
Psychiatric disorders	Frequent: Impaired concentration, anxiety, nervousness, euphoria, confusion, somnolence, amnesia, abnormal thinking or dreaming Frequency unknown: Aggressive behaviour, suicidal thoughts or attempts	Frequent: Anxiety, headaches Less frequent: Abnormal dreams Frequency unknown: Depression, insomnia	Frequent: Depression, insomnia, abnormal dreams
Nervous system disorders	Frequent: Headache, dizziness, insomnia Less frequent: Hypoaesthesia, convulsions, depersonalisation, paraesthesia, nervousness	Less frequent: Paraesthesia, peripheral neuropathy, anxiety, insomnia, dizziness, headache	Frequent: Somnolence, headache, dizziness
Ear and labyrinth disorders	Less frequent: Tinnitus		
Respiratory, thoracic and	Frequency unknown: Dyspnoea	Frequent: Cough, rhinitis, pneumonia	

mediastinal disorders		Less frequent: Dyspnoea	
Gastrointestinal disorders	Frequent: Dyspepsia, abdominal pain, pancreatitis, diarrhoea, nausea, vomiting Frequency unknown: Constipation, malabsorption	Frequent: Dyspepsia, abdominal pain, diarrhoea, nausea, vomiting, flatulence Less frequent: Pancreatitis	Frequent: Diarrhoea, nausea, vomiting
Hepato-biliary disorders	Frequent: Raised liver enzymes Frequency unknown: Hepatic failure	Less frequent: Hepatotoxicity Frequency unknown: Hepatitis	
Skin and subcutaneous tissue disorders	Frequent: Pruritis, skin rash Less frequent: Erythema multiforme, Stevens-Johnson syndrome, photoallergic dermatitis, skin discolouration	Frequent: Rash event, pruritis Less frequent: Hyperpigmentation of soles and/or palms, maculopapular and vesiculobullous rash, urticaria	Frequent: Rash
Musculoskeletal, connective tissue and bone disorders	Frequent: Arthralgia, myalgia Frequency unknown: Myopathy	Frequent: Back pain, bone density decreased (see section 4.4) Less frequent: Myalgia, bone pain, osteomalacia, arthralgia, myopathy	
Renal and urinary disorders		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	Frequency unknown: Fatigue	Frequency unknown: Fatigue	Frequent: Fatigue

Investigations	Less frequent: Raised serum cholesterol and triglycerides, raised serum amylases	Frequency unknown: Elevations of bilirubin, pancreatic amylase, serum glucose, urine glucose, raised serum amylase, hypophosphataemia, raised liver enzymes	Frequency unknown: Laboratory abnormalities related to fasting cholesterol, creatine kinase, serum amylase, alkaline phosphatise, AST, ALT, haemoglobin, hyperglycaemia, haematuria, neutrophils, fasting triglycerides, hypertriglyceridemia, hypercholesterolaemia, insulin resistance, hyperlactataemia, hyperlipidaemia

Table 4: Side effects reported from post-marketing surveillance of TEEVIR

System Organ Class	Efavirenz	Tenofovir	Emtricitabine
Immune system disorders	Allergic reactions, immuno-allergic liver injury failure	Allergic reactions	No additional events have been identified for inclusion in this section.
Endocrine disorders	Gynaecomastia		
Metabolism and nutrition disorders	Redistribution/ accumulation of body fat (see section 4.4), hypercholesterolaemia, hypertriglyceridemia	Hypophosphataemia, lactic acidosis	
Psychiatric disorders	Aggressive reactions, agitation, delusions, emotional lability, mania, neurosis, paranoia, psychosis, suicide		
Nervous system disorders	Abnormal co-ordination, ataxia, convulsions, hypoesthesia, tremor		
Eye disorders	Abnormal vision		

Ear and labyrinth disorders	Tinnitus		
Cardiac disorders	Palpitations		
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Dyspnoea	
Gastrointestinal disorders	Constipation, malabsorption		
Hepato-biliary disorders	Hepatic enzyme increases in hepatic failure, hepatitis	Increased liver enzymes, hepatitis	
Skin and subcutaneous tissue disorders	Flushing, erythema multiforme, nail disorders, photoallergic dermatitis, skin discolouration, Stevens-Johnson syndrome	Rash	
Musculoskeletal, connective tissue and bone disorders	Myopathy	Myopathy, osteomalacia (both associated with proximal renal tubulopathy)	
Renal and urinary disorders		Renal insufficiency, renal failure, acute renal failure, Fanconi syndrome, proximal tubulopathy, proteinuria, increased creatinine, acute tubular necrosis, nephrogenic diabetes insipidus, polyuria, interstitial nephritis (including acute cases)	

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. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.
Suspected adverse reactions can also be reported directly to the HCR via email: pv@innovata.co.za or tel: +27 86 999 0912

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) C_{max} (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 (C_{max})

were achieved in 1,0 ± 0,4 hours, mean (± SD) C_{max}.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 ^{14}C-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 C_{max} of efavirenz by 28 % and 79 %, respectively, compared to administration in a fasted state. Compared to fasted administration, dosing of tenofovir disoproxil fumarate and emtricitabine in combination with either a high fat meal or a light meal increased the mean AUC and C_{max} of tenofovir by 35 % and 15 %, respectively without affecting emtricitabine exposures.

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, C_{max} and $AUC_{o-\alpha}$ 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,

100 NORTHERN PARKWAY, ORMONDE

JHB, 2091

+27 86 999 0912

8 REGISTRATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION TEEVIR

02/04/2020

10 DATE OF REVISION OF THE TEXT TEEVIR

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