Professional information for medicines for human use

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 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 C_{max} of efavirenz and significant decreases in the AUC and C_{max} 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

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
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

5.1 Pharmacodynamic properties
Class of medicine: A 20.2.8 Antiviral agents

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. **ATROIZA** 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 $_{0-\alpha}$ 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 3 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 and 30'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 and 30's.

6.6 Special precautions for disposal and other handling
No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION
MYLAN (PTY) LTD
Building 6, Greenstone Hill Office Park
Emerald Boulevard
MODDERFONTEIN, 1645
Republic of South Africa

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