**SCHEDULING STATUS**

**S4**

## 1. NAME OF THE MEDICINE

**TRIOVIR 600 mg/200 mg/ 245 mg (film-coated tablets)**

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-tablet contains 600mg of efavirenz, 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate (DF) (which is equivalent to 245 mg of Tenofovir) as active ingredients.

*Excipients with known effect:*

Each film coated tablet:

Contains sugar: Lactose120 mg

Contains: Sodium 7.73 mg

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

For the full list of excipients, see section 6.1.

**LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANOLOGUES ALONE OR IN COMBINATION WITH OTHER ANTI- RETROVIRALS (*SEE SECTION 4.4*). EARLY SYMPTOMS (SYMPTOMATIC HYPERLACTATAEMIA) INCLUDE BENIGN DIGESTIVE SYMPTOMS (NAUSEA, VOMITING AND ABDOMINAL PAIN), NON-SPECIFIC MALAISE, LOSS OF APPETITE, WEIGHT LOSS, RESPIRATORY SYMPTOMS (RAPID AND/OR DEEP BREATHING) OR NEUROLOGICAL SYMPTOMS (INCLUDING MOTOR WEAKNESS). LACTIC ACIDOSIS HAS A HIGH MORTALITY AND MAY BE ASSOCIATED WITH PANCREATITIS, LIVER FAILURE OR RENAL FAILURE. LACTIC ACIDOSIS GENERALLY OCCURRED AFTER A FEW OR SEVERAL MONTHS OF TREATMENT. TREATMENT WITH TRIOVIR SHOULD BE DISCONTINUED IN THE SETTING OF**

**SYMPTOMATIC HYPERLACTATAEMIA AND METABOLIC/LACTIC ACIDOSIS, PROGRESSIVE HEPATOMEGALY, OR RAPIDLY ELEVATING AMINOTRANSFERASE LEVELS.**

**CAUTION SHOULD BE EXERCISED WHEN ADMINISTERING TRIOVIR TO ANY PATIENT (PARTICULARLY OBESE WOMEN) WITH HEPATOMEGALY, HEPATITIS OR OTHER KNOWN RISK FACTORS FOR LIVER DISEASE AND HEPATIC STEATOSIS (INCLUDING CERTAIN MEDICINES AND ALCOHOL). PATIENTS CO-INFECTED WITH HEPATITIS C AND TREATED WITH ALPHA-INTERFERON AND RIBAVIRIN MAY CONSTITUTE A SPECIAL RISK.**

**PATIENTS AT INCREASED RISK SHOULD BE FOLLOWED CLOSELY.**

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

## 3. PHARMACEUTICAL FORM

Film-coated tablets.

Pink coloured, capsule shaped, film-coated tablets of dimensions 22 mm x 10 mm, debossed with "M171" on one side and plain on the other side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

TRIOVIR is indicated for use alone as a complete regimen or in combination with other anti-retroviral medicines for the treatment of HIV-1 infection in adults.

## 4.2 Posology and method of administration

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

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

*Adults:* The dose of TRIOVIR is one tablet once daily taken orally on an empty stomach. Dosing at bedtime may improve the tolerability of nervous system symptoms.

**Special populations**

*Paediatric population***:** TRIOVIR is not recommended for use in patients less than 18 years of age.
*Renal Impairment***:** Because TRIOVIR is a fixed-dose combination, it should not be prescribed for patients requiring dosage adjustment such as those with moderate or severe renal impairment (creatinine clearance less than 50 ml/min)- (*see sections 4.3 and 4.4*).

## 4.3 CONTRAINDICATIONS

- TRIOVIR is contraindicated in patients with previously demonstrated hypersensitivity to tenofovir, emtricitabine, effavirenz or any of the excipients of the TRIOVIR listed in section 6.1.
- TRIOVIR should not be administered concurrently with terfenadine astemizole, peridil, cisapride, midazolam, pimozide, triazolam or ergot derivatives (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine), because competition for CYP3A4 by efavirenz could result in inhibition of metabolism of these medicines and create the

potential for serious and/or life-threatening adverse events (e.g. cardiac dysrhythmias, prolonged sedation or respiratory depression).

- TRIOVIR should not be administered concurrently with voriconazole because efavirenz significantly decreases voriconazole plasma concentrations *(see section 4.5*).
- TRIOVIR is contraindicated in patients with moderate to severe renal impairment [Creatinine clearance less than 50 ml/min (*see sections 4.4 and 5.2*).
- History of previous liver injury/failure with efavirenz-containing antiretroviral treatment (ART)
- 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 dysrhythmias or with clinically relevant bradycardia or with congestive cardiac failure accompanied by reduced left ventricle ejection fraction.
    - severe disturbances of electrolyte balance e.g., hypokalaemia or hypomagnesaemia.
- Co-administration with medicines that are known to prolong the QTc interval (prodysrhythmic):
    - *These medicines include:*
    - antidysrhythmics of classes IA and III,
    - neuroleptics, antidepressive medicines,
    - certain antibiotics including some medicines of the following classes: macrolides, fluoroquinolones, imidazole and triazole antifungal medicines,
    - certain non-sedating antihistamines (terfenadine, astemizole),
    - cisapride,
    - flecainide,
    - certain antimalarials,

- methadone (*see sections 4.5*).

- Pregnancy and lactation *(see section 4.6*).
- Children less than 18 years of age.
- Co-administration with elbasvir/grazoprevir due to the expected significant decreases in plasma concentrations of elbasvir and grazoprevir. This effect is due to induction of CYP3A4 or P-gp by efavirenz and may result in loss of therapeutic effect of elbasvir/grazoprevir (*see section 4.5)*.
- Co-administration with herbal preparations containing St. John's wort (*Hypericum perforatum*) due to the risk of decreased plasma concentrations and reduced clinical effects of efavirenz (*see section 4.5*).
- TRIOVIR must not be used concomitantly with medicines containing any of the components efavirenz, emtricitabine or tenofovir, or who concomitantly take other cytidine analogues, such as lamivudine and adefovir dipivoxil (*see section 4.5*).

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

***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 positive patients.

Clinical examination should include evaluation for physical signs of fat redistribution. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

***Co-administration with Related Medicines***

Related medicines not for co-administration with TRIOVIR include emtricitabine, tenofovir disoproxil fumarate, emtricitabine/tenofovir disoproxil fumarate and efavirenz, which contain the same active components as TRIOVIR. Due to similarities between emtricitabine and lamivudine, TRIOVIR should not be co-administered with medicines containing lamivudine, including

lamivudine/zidovudine, lamivudine, abacavir sulphate/lamivudine or abacavir sulphate/lamivudine/zidovudine.

Since emtricitabine and tenofovir are primarily eliminated by the kidneys, co-administration of TRIOVIR 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.

***Pancreatitis***

Pancreatitis has been observed in some patients receiving tenofovir emtricitabine and efavirenz as in TRIOVIR.

Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of TRIOVIR until diagnosis of pancreatitis is excluded.

***Lactic acidosis / hyperlactataemia***

Use of TRIOVIR 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 TRIOVIR to patients with known risk factors for liver disease.

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

***Switching from a PI-based antiretroviral regimen***

Currently available data indicate a trend that in patients on a PI-based antiretroviral regimen the switch to TRIOVIR may lead to a reduction of the response to the therapy *(see section 5.1)*. These patients should be carefully monitored for rises in viral load and, since the safety profile of efavirenz differs from that of protease inhibitors, for adverse reactions.

***Opportunistic Infections***

Patients receiving TRIOVIR 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 TRIOVIR, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination.

Appropriate precautions should continue to be employed.

***Effect of food***

The administration of TRIOVIR with food may increase efavirenz exposure (*see section 5.2)* and may lead to an increase in frequency of adverse reactions (*see section 4.8*). It is recommended that TRIOVIR be taken on an empty stomach, preferably at bedtime.

***Liver disease***

Use of TRIOVIR can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of TRIOVIR 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.

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 a high morbidity / mortality risk and may present many months after therapy has been initiated or even stopped. Risk factors include younger age, CD4 + counts ≥ 350 cells/microliters and female gender.

Patients on TRIOVIR or efavirenz containing ART should be regularly monitored for jaundice (including a laboratory bilirubin and liver enzymes) and bleeding tendencies.

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

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

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

***Hepatic events***

Post-marketing reports of hepatic failure also occurred in patients with no pre-existing hepatic disease or other identifiable risk factors (*see section 4.8*). Liver enzyme monitoring should be considered for all patients independent of pre-existing hepatic dysfunction or other risk factors.

***Patients with HIV and Hepatitis B or C virus co-infection***

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

Medical practitioners should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV).

In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant professional information for these medicines.

Patients co-infected with HIV and HBV who discontinue TRIOVIR 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 therapy in patients co-infected with HIV and HBV may be associated with severe, acute exacerbations of hepatitis.

***QTc Prolongation***

QTc prolongation has been observed with the use of efavirenz (*see sections 4.5 and 5.1)*. For patients at increased risk of Torsade de Pointes or who are receiving medicines with a known risk for Torsade de Pointes, consider alternatives to TRIOVIR.

***Psychiatric Symptoms***

Serious psychiatric adverse experiences have been reported in patients treated with efavirenz. Patients should be advised that should they experience symptoms such as severe depression, psychosis or suicidal ideation and catatonia, they should contact their doctor immediately to assess the possibility that the symptoms may be related to the use of efavirenz, and if so, to determine whether the risk of continued therapy outweighs the benefits (*see section 4.8*)

***Nervous system symptoms***

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

Symptoms including, but not limited to, dizziness, insomnia, somnolence, impaired concentration and abnormal dreaming are frequently reported undesirable effects in patients receiving efavirenz 600 mg daily in clinical studies. Dizziness was also seen in clinical studies with emtricitabine and

tenofovir disoproxil. Headache has been reported in clinical studies with emtricitabine (see section 4.8).

Nervous system symptoms associated with efavirenz usually begin during the first one or two days of therapy and generally resolve after the first two to four weeks. Patients should be informed that if they do occur, these common symptoms are likely to improve with continued therapy and are not predictive of subsequent onset of any of the less frequent psychiatric symptoms. Dosing at bedtime may improve the tolerability of these nervous system symptoms (*see sections 4.2 and 4.8*).

Patients receiving TRIOVIR should be alerted to the potential for additive central nervous system effects when TRIOVIR is used concomitantly with alcohol or psycho-active medicines.

***Late Onset Neurotoxicity***

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

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

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

***Convulsions***

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

***Renal Impairment* (*see section 4.3*)**

Emtricitabine and tenofovir are principally eliminated by the kidney, however efavirenz is not. Since TRIOVIR is a combination product and the dose of the individual components cannot be altered, patients with creatinine clearance less than 50 ml/min should not receive TRIOVIR**.**

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

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 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 TRIOVIR**.** Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment.

TRIOVIR should be avoided with concurrent or recent use of a nephrotoxic medicine.

***Bone Effects***

In a 144·week study of treatment naive patients, decreases in bone mineral density (BMD) were seen at the lumbar spine and hip in both 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 receiving tenofovir disoproxil fumarate + lamivudine + efavirenz compared with patients receiving stavudine + lamivudine + efavirenz. Changes in BMD at the hip were similar between the two treatment groups.

The majority of the reduction in bone mineral density (BMD) occurred in the first 24 to 48 weeks and this reduction is sustained through 144 weeks. Twenty-eight percent of tenofovir disoproxil fumarate treated patients versus 21 % of the comparator patients lost at least 5 % of BMD at the spine or 7 % BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 patients in the tenofovir disoproxil fumarate and 6 patients in the stavudine group. Tenofovir disoproxil fumarate was associated with significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide and urinary N-telopeptide, suggesting increased bone turnover. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in patients receiving tenofovir disoproxil fumarate. The effects of tenofovir disoproxil fumarate associated changes in BMD and biochemical

markers on long-term bone health and future fracture risk are unknown. For additional information, please consult the tenofovir disoproxil fumarate professional information.

Cases of osteomalacia (associated with proximal renal tubulopathy) have been reported in association with the use of tenofovir disoproxil fumarate (*see section 4.8*).

Bone monitoring should be considered for HIV infected patients who have a history of pathologic bone fracture or are at risk for osteopenia. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected, then appropriate consultation should be obtained.

***Skin Rash***

*Efavirenz*: It was reported that patients experienced new-onset skin rash compared with patients treated in control groups. Rash associated with blistering, moist desquamation or ulceration occur in 0,9 % of patients treated with efavirenz. Grade 4 rash (e.g. erythema multiforme, Stevens-Johnson syndrome) in patients treated with efavirenz is 0,1 %. Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first 2 weeks of initiating therapy with efavirenz (median time to onset of rash in adults was 11 days) and therefore, in most patients continuing therapy with efavirenz, rash resolves within 1 month (median duration, 16 days. TRIOVIR can be reinitiated in patients interrupting therapy because of rash. TRIOVIR should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash.

***Weight and metabolic parameters***

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

***Mitochondrial dysfunction***

Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. 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 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 sign and symptoms.

***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, focal atypical mycobacterial infections, cytomegalovirus retinitis, cryptococcal meningitis, and *Pneumocydtis jirovecii* (*carinii*) pneumonia (PCP).

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, polymyositis, Guillain-Barre Syndrome and autoimmune hepatitis) have also been reported as IRIS reactions; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

***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.

***Patients with HIV-1 harbouring mutations***

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

***Cholesterol***

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

***Elderly***

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

***Paediatric Use***

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

***Excipients***

TRIOVIR contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, total lactase deficiency or glucose-galactose malabsorption should not take TRIOVIR.

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

***Liver Enzymes***

In patients with 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 (*see section 4.4, Patients Co-infected with HIV and HBV*).

In patients with persistent elevations of serum transaminases to greater than five times the upper limit of the normal range, the benefit of continued therapy with TRIOVIR needs to be weighed against the unknown risks of significant liver toxicity.

***Co-administration with other medicinal products***

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

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

**4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION**

**Efavirenz:** Efavirenz has been shown *in vivo* to induce CYP3A4. Other medicines that are substrates of CYP3A4 may have decreased plasma concentrations when co-administered with efavirenz. *In vitro* studies have demonstrated that efavirenz inhibits 2C9, 2C19 and 3A4 isozymes in the range of observed efavirenz plasma concentrations. Co-administration of efavirenz with medicines primarily metabolised by these isozymes may result in altered plasma concentrations of the co-administered medicine. Therefore, appropriate dose adjustments may be necessary for these medicines.

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

**Emtricitabine and tenofovir disoproxil fumarate:** Since emtricitabine and tenofovir are primarily eliminated by the kidneys, co-administration of TRIOVIR 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, aciclovir, adefovir, dipivoxil, cidofovir, ganciclovir, valacyclovir and valganciclovir.

Co-administration of tenofovir disoproxil fumarate and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse events. Didanosine should be discontinued in patients who develop didanosine-associated adverse events (for didanosine dosing adjustment recommendations, see Table 2 in section 4.5). Suppression of CD4 cell counts has been observed in patients receiving tenofovir disoproxil fumarate with didanosine at a dose of 400 mg daily.

Atazanavir and lopinavir/ritonavir have been shown to increase tenofovir concentrations. The mechanism of this interaction is unknown. Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders. Patients receiving either atazanavir or lopinavir/ritonavir with tenofovir disoproxil fumarate should be monitored for tenofovir-associated adverse events. TRIOVIR should be discontinued in patients who develop tenofovir-associated adverse events (for atazanavir dosing adjustment recommendations, see Table 2 in section 4.5).

Other important medicine interaction information for TRIOVIR is summarised in Table 1 and 2. The medicine interactions described are based on studies conducted with efavirenz, emtricitabine or tenofovir disoproxil fumarate as individual agents or are potential medicine interactions; no medicine interaction studies have been conducted using TRIOVIR. The tables include potentially significant interactions but are not all inclusive.

**Table 1:**

**Medicines that are contraindicated or not recommended for use with Efavirenz:**

| **Medicine Class: Medicine Name** | **Clinical Comment:** |
|---|---|
| Antifungal: Voriconazole | Contraindicated because efavirenz significantly decreases voriconazole plasma concentrations, and co-administration may decrease the therapeutic effectiveness of voriconazole. Also, voriconazole significantly increases efavirenz plasma concentrations, which may increase the risk of efavirenz-associated side effects. |

| | |
|---|---|
| Antihistamine: Astemizole, terfenadine | Contraindicated due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias. |
| Antimigraine: Ergot derivatives | Contraindicated due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterised by peripheral vasospasm and ischaemia of the extremities and other tissues. |
| Antiretrovirals: emtricitabine, tenofovir, efavirenz, lamivudine | Not for use with TRIOVIR because emtricitabine, tenofovir disoproxil fumarate, emtricitabine/tenofovir disoproxil fumarate and efavirenz are components of TRIOVIR.<br>Lamivudine is similar to emtricitabine. |
| Benzodiazepines: midazolam, triazolam | Contraindicated due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression. |
| Calcium channel blocker:<br>Bepridil | Contraindicated due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias |
| GI motility medicine: cisapride | Contraindicated due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias. |
| Neuroleptic: pimozide | Contraindicated due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias. |
| St John's Wort<br>(*Hypericum perforatum* | Not recommended: Expected to substantially decrease plasma levels of efavirenz; has not been studied in combination with efavirenz. |
| **Hepatitis C antivirals:**<br>Elbasvir / Grazoprevir + Efavirenz | Elbasvir:<br>AUC: ↓ 54%<br>Cmax: ↓ 45%<br>(CYP3A4 or P-gp induction – effect on elbasvir)<br>Grazoprevir:<br>AUC: ↓ 83%<br>Cmax: ↓ 87%<br>(CYP3A4 or P-gp induction – effect on grazoprevir)<br>Efavirenz:<br>AUC: ↔<br>Cmax: ↔<br>Co-administration of TRIOVIR with elbasvir/grazoprevir is contraindicated because it may lead to loss of virologic response to elbasvir/grazoprevir.<br>This loss is due to significant decreases in elbasvir/grazoprevir plasma concentrations caused by CYP3A4 or P-gp induction. |

**Table 2**

**Established and Other Potentially Significant Interactions: Alteration in Dose or Regimen May Be Recommended Based on Interaction Studies or Predicted Interaction.**

| Concomitant Medicine Class: Medicine Name | Effect | Clinical Comment |
|---|---|---|
| *Antiretroviral Agents* | | |
| Protease Inhibitor: Amprenavir | ↓amprenavir concentration | Efavirenz has the potential to decrease serum concentrations of amprenavir |
| Protease inhibitor: Fosamprenavir calcium | ↓amprenavir concentration | Fosamprenavir (unboosted): Appropriate doses of fosamprenavir and TRIOVIR with respect to safety and efficacy have not been established.<br>Fosamprenavir/ritonavir: An additional 100 mg/day (300 mg total) of ritonavir is recommended when TRIOVIR is administered with fosamprenavir/ritonavir once daily. No change in ritonavir dose is required when TRIOVIR is administered with fosamprenavir plus ritonavir twice daily. |
| Protease Inhibitor: Atazanavir | ↓atazanavir concentration<br>↑tenofovir concentration | Plasma concentrations of atazanavir were decreased by both efavirenz and tenofovir disoproxil fumarate. Sufficient data are not available to make a dosing recommendation for atazanavir or atazanavir/ritonavir with TRIOVIR. Therefore, co-administration of TRIOVIR and atazanavir is not recommended due to concerns regarding decreased atazanavir concentrations. |
| Protease Inhibitor: Indinavir | ↓indinavir concentration | The optimal dose of indinavir, when given in combination with efavirenz, is not known. Increasing the indinavir dose to 1 000 mg every 8 hours does not compensate for the increased indinavir metabolism due to efavirenz |
| Protease Inhibitor: Lopinavir/ritonavir | ↓lopinavir concentration<br>↑tenofovir concentration | A dose increase of lopinavir/ritonavir to 600/150 mg (3 tablets) twice daily may be considered when used in combination with efavirenz in treatment-experienced patients where decreased susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence).<br>Patients should be monitored for tenofovir-associated adverse events. TRIOVIR should be discontinued in patients who develop tenofovir-associated adverse events. |

| | | |
|---|---|---|
| Protease Inhibitor:<br>ritonavir | ↑ritonavir concentration<br>↑efavirenz concentration | When ritonavir 500 mg every 12 hours was co-administered with efavirenz 600 mg once daily, the combination was associated with a higher frequency of adverse clinical experiences (e.g. dizziness, nausea, paraesthesia) and laboratory abnormalities (elevated liver enzymes).<br>Monitoring of liver enzymes is recommended when TRIOVIR is used in combination with ritonavir. |
| Protease Inhibitor:<br>saquinavir | ↓saquinavir concentration | Should not be used as sole protease inhibitor in combination with TRIOVIR**.** |
| NRTI:<br>didanosine | ↑didanosine concentration | Higher didanosine concentrations could potentiate didanosine-associated adverse events, including pancreatitis, and neuropathy. In adults weighing > 60 kg, the didanosine dose should be reduced to 250 mg if co-administered with TRIOVIR. Data are not available to recommend a dose adjustment of didanosine for patients weighing < 60 kg. When co-administered, TRIOVIR and didanosine must be taken under fasted conditions or with a light meal (< 400 kcal, 20 % fat). Co-administration of didanosine buffered formulation with TRIOVIR should be under fasted conditions. Co-administration of TRIOVIR and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse events. For additional information, please consult the didanosine professional information. |
| Other agents: | | |
| Anticoagulant:<br>warfarin | ↑ or ↓ warfarin concentration | Plasma concentrations and effects (INR) potentially increased or decreased by efavirenz |
| Anticonvulsants: phenytoin<br>phenobarbitone | ↓Anticonvulsant concentration<br>↓efavirenz concentration | Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted |
| Carbamazepine | ↓ carbamazepine concentration<br>↓ efavirenz concentration | There is insufficient data to make a dose recommendation for TRIOVIR. |

| | | |
|---|---|---|
| | | Alternative anticonvulsant treatment should be used. |
| Antidepressant:<br>sertraline | ↓sertraline concentration | Increase in sertraline dose should be guided by clinical response. |
| Antifungals:<br>Itraconazole<br><br><br><br>Ketoconazole | ↓itraconazole[1] concentration<br>↓hydroxy-itraconazole[1] concentration<br>↓ketoconazole[1] concentration | Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered.<br>Medicine interaction studies with TRIOVIR and ketoconazole have not been conducted. Efavirenz has the potential to decrease plasma concentrations of ketoconazole. |
| Anti-infective:<br>clarithromycin | ↓clarithromycin concentration<br>↑14-OH metabolite concentration | Clinical significance unknown. In uninfected volunteers, 46 % developed rash while receiving efavirenz and clarithromycin. No dose adjustment of TRIOVIR is recommended when given with clarithromycin. Alternatives to clarithromycin, such as azithromycin, should be considered. Other macrolide antibiotics, such as erythromycin, have not been studied in combination with TRIOVIR. |
| Antimycobacterial:<br>rifabutin | ↓rifabutin concentration | Increased daily dose of rifabutin by 50 %. Consider doubling rifabutin dose in regimens where rifabutin is given 2 or 3 times a week. |
| Antimycobacterial:<br>rifampicin | ↓efavirenz[1] concentration | Clinical significance of reduced efavirenz concentration is unknown. Dosing recommendations for concomitant use of TRIOVIR and rifampicin have not been established. |
| Calcium channel blockers:<br>Diltiazem<br><br><br>Others (e.g. felodipine, nicardipine, nifedipine, verapamil) | ↓diltiazem[1] concentration<br>↓desacetyl diltiazem[1] concentration<br>↓N-monodes-methyl diltiazem[1] concentration<br>↓calcium channel blocker | Diltiazem dose adjustments should be guided by clinical response (refer to professional information for diltiazem). No dose adjustments of TRIOVIR.<br>No data are available on the potential interactions of efavirenz with other calcium channel blockers that are substrates of the CYP3A4 enzyme. The potential exists for reduction in plasma concentrations of the calcium channel blocker. Dose adjustments should be guided by clinical response (refer to the professional information for the calcium channel blocker). |
| HMG-CoA reductase inhibitors:<br>Atorvastatin | ↓atorvastatin[1] concentration<br>↓pravastatin[1] concentration | Plasma concentrations of atorvastatin, pravastatin, and |

| | | |
|---|---|---|
| pravastatin<br>simvastatin | ↓simvastatin[1] concentration | simvastatin decreased with efavirenz. Consult the professional information for the HMG-CoA reductase inhibitor for guidance on individualising the dose |
| Narcotic analgesic:<br>methadone | ↓methadone concentration | Co-administration of efavirenz in HIV-infected individuals with a history of injection medicine use resulted in decreased plasma levels of methadone and signs of opiate withdrawal. Methadone dose was increased by a mean of 22 % to alleviate withdrawal symptoms. Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms. |
| Oral contraceptive:<br>Ethinyl oestradiol | ↑ethinyl estradiol concentration | Clinical significance unknown. Because the potential interaction of efavirenz with oral contraceptives has not been fully characterised, a reliable method of barrier contraception should be used in addition to oral contraceptives. |

**Efavirenz Assay Interference**

**Cannabinoid Test Interaction:** Efavirenz does not bind to cannabinoid receptors. False-positive urine cannabinoid test results have been observed in non-HIV-infected volunteers receiving efavirenz when Microgenics Cedia DAU Multi-Level THC assay was used for screening. Negative results were obtained when more specific confirmatory testing was performed with gas chromatography/mass spectrometry. For more information, please consult the efavirenz professional information.

**Other Interactions**

**Efavirenz**

Medicine interaction studies were performed with efavirenz and other medicines likely to be co-administered or medicines commonly used as probes for pharmacokinetic interaction. There was no clinically significant interaction observed between efavirenz and zidovudine, lamivudine, azithromycin, fluconazole, lorazepam, cetrizine or paroxetine. Single doses of famotidine or an aluminium and magnesium antacid with simethicone had no effects of efavirenz exposures.

**Emtricitabine and tenofovir disoproxil fumarate**

No clinically significant medicine interactions have been observed between emtricitabine and famciclovir, indinavir, stavudine, tenofovir disoproxil fumarate and zidovudine. Similarly, no clinically significant medicine interactions have been observed between tenofovir disoproxil fumarate and abacavir, adefovir, dipivoxil, efavirenz, emtricitabine, indinavir, lamivudine, lopinavir/ritonavir, methadone, nelfinavir, oral contraceptives, ribavirin and saquinavir/ritonavir in studies conducted in healthy volunteers.

Following multiple dosing to HIV-negative subjects receiving either chronic methadone maintenance therapy, oral contraceptives or single doses of ribavirin, steady-state tenofovir pharmacokinetics were similar to those observed in previous studies, indicating a lack of clinically significant medicine interactions between these agents and tenofovir disoproxil fumarate.

## 4.6 FERTILITY, PREGNANCY AND LACTATION

**Pregnancy:**

Efavirenz is teratogenic and may cause foetal harm when administered during the first trimester of pregnancy. There have been reports of congenital abnormalities including neural tube defects and meningomyelocele in babies exposed in utero to efavirenz during the first trimester of pregnancy.

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

If a patient is to be treated with TRIOVIR, pregnancy should be excluded 24 hours prior to initiation of treatment. A medically/laboratory supervised pregnancy/urine test should be done to exclude pregnancy and repeated at frequent intervals during treatment to exclude pregnancy.

Late onset neurological disorders relating to mitochondrial dysfunction have been observed in children who have been exposed in utero and/or postnatally to nucleoside analogues as contained in TRIOVIR. Studies of efavirenz in animals have shown reproductive toxicity including marked teratogenic effects.

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

There are no adequate and well-controlled studies of efavirenz, emtricitabine and tenofovir as contained in TRIOVIR in pregnant women.

**Breastfeeding**

**It is recommended that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV.**

Studies in rat have demonstrated that both efavirenz and tenofovir are secreted in milk. It is not known whether efavirenz, emtricitabine or tenofovir is excreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving** TRIOVIR.

**Fertility**

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

## 4.7 EFFECTS ON THE ABILITY TO DRIVE AND USE MACHINES

TRIOVIR may cause dizziness.

Efavirenz may also cause impaired concentration and/or somnolence. Patients should be instructed that if they experience these symptoms, they should avoid potentially hazardous tasks such as driving and operating machinery, until they know how treatment with TRIOVIR affects them.

## 4.8 UNDESIRABLE EFFECTS

### a. Summary of the safety profile

The combination of efavirenz, emtricitabine and tenofovir disoproxil has been studied either as the fixed-dose combination tablet or as the component products.

Adverse reactions were generally consistent with those seen in previous studies of the individual components. The most frequently reported adverse reactions among patients treated up to 48 weeks were psychiatric disorders (16 %), nervous system disorders (13 %), and gastrointestinal disorders (7 %).

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

Less Frequent events of renal impairment, renal failure, proximal renal tubulopathy (including Fanconi syndrome) sometimes leading to bone abnormalities (infrequently contributing to fractures) have also been reported. Monitoring of renal function is recommended for patients receiving TRIOVIR (*see section 4.4*).

Discontinuation of TRIOVIR therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis (*see section 4.4*).

The administration of TRIOVIR with food may increase efavirenz exposure and may lead to an increase in the frequency of adverse reactions (*see sections 4.4 and 5.2)*.

**Tabulated list of adverse reactions**

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

Frequent:

- Anorexia

Less frequent:

- Dry mouth

- Incoherent speech
- Increased appetite
- Libido decreased
- Myalgia

Adverse reactions that may result associated with individual components efavirenz emtricitabine and tenofovir disoproxil as in TRIOVIR

| | **Efavirenz** | **Emtricitabine** | **Tenofovir disoproxil** |
|---|---|---|---|
| ***Blood and lymphatic system disorders:*** | | | |
| Frequent | | neutropenia | |
| Less frequent | | anaemia[1] | |
| ***Immune system disorders:*** | | | |
| Frequent | | allergic reaction | |
| | **Efavirenz** | **Emtricitabine** | **Tenofovir disoproxil** |
| Less frequent | hypersensitivity | | Allergic reaction (including angioedema |
| Frequency not known | Immuno-allergic liver injury/failure | | |
| ***Metabolism and nutrition disorders:*** | | | |
| Frequent | hypertriglyceridaemia[3] | hyperglycaemia, hypertriglyceridaemia | hypophosphataemia[2] |
| Less frequent | hypercholesterolaemia[3] | | hypokalaemia[2] lactic acidosis |
| Frequency unknown | Redistribution/accumulation of body fat | | |
| ***Psychiatric disorders:*** | | | |
| Frequent | depression (severe in 1.6%)[3], anxiety[3], abnormal dreams[3], insomnia[3] | abnormal dreams, insomnia, depression | insomnia abnormal dreams depression |
| Less frequent | suicide attempt[3], suicide ideation[3], psychosis[3], mania[3], paranoia[3], hallucination[3], euphoric mood[3], affect lability[3], confusional state[3], aggression[3], catatonia[3] completed suicide[3,4], delusion[3,4], neurosis[3,4] | | |
| Frequency not known | ataxia, hyper-somnolence, encephalopathy, coma and agitation | | |
| ***Nervous System Disorders:*** | | | |
| Frequent | cerebellar coordination and balance disturbances[3], somnolence (2.0%)[3], headache (5.7%)[3], disturbance in attention (3.6%)[3], dizziness (8.5%) | headache dizziness, somnolence | headache dizziness, somnolence |

| | | | |
|---|---|---|---|
| Less frequent | convulsions[3], amnesia[3], thinking abnormal[3], ataxia[3], coordination abnormal[3], agitation[3], tremor | | |
| | **Efavirenz** | **Emtricitabine** | **Tenofovir disoproxil** |
| Frequency unknown | hypoaesthesia abnormal coordination neuropathy | | |
| | | | |
| ***Eye Disorders:*** | | | |
| Less frequent | blurred vision | | |
| ***Ear and labyrinth disorders:*** | | | |
| Less frequent | tinnitus, vertigo | | |
| ***Cardiac disorders*** | | | |
| Frequency unknown | palpitations | | |
| **Vascular disorders:** | | | |
| Less frequent | flushing | | |
| ***Repiratory, thoracic and mediastinal disorders*** | | | |
| Frequency Unknown | dyspnoea | | dyspnoea |
| ***Gastrointestinal disorders:*** | | | |
| Frequent | diarrhoea, vomiting, abdominal pain, nausea | diarrhoea, nausea elevated amylase including elevated pancreatic amylase, elevated serum lipase, vomiting, abdominal pain, dyspepsia | diarrhoea, vomiting, nausea abdominal pain, abdominal distension, flatulence |
| Less frequent | pancreatitis | | pancreatitis |
| Frequency unknown | constipation malabsorption | | increased amylase |
| ***Hepatobiliary disorders:*** | | | |
| Frequent | elevated aspartate aminotransferase (AST), elevated alanine aminotransferase (ALT), elevated gammaglutamyltransferase (GGT) | elevated serum AST and/or elevated serum ALT, hyperbilirubinaemia | increased transaminases (AST and ALT) |
| Less frequent | hepatitis acute hepatic failure[3,4] | | hepatic steatosis, hepatitis |
| ***Skin and subcutaneous tissue disorders:*** | | | |
| Frequent | rash (moderate-severe, 11.6%, all grades, 18%)[3] pruritus | vesiculobullous rash, pustular rash, maculopapular rash, rash, pruritus, urticaria, skin discolouration (increased | rash |
| | **Efavirenz** | **Emtricitabine** | **Tenofovir disoproxil** |
| | | pigmentation)[1] | |
| Less frequent | Stevens-Johnson syndrome, erythema multiforme[3], severe rash (< 1%), photoallergic dermatitis | | (see ***immune system disorders*** |
| Frequency unknown | flushing, nail disorders, skin discolouration | | pruritus |
| ***Musculoskeletal and connective tissue disorders:*** | | | |
| Frequent | | elevated creatine kinase | |

| | | | |
|---|---|---|---|
| Less frequent | | | rhabdomyolysis[2], muscular weakness[2] osteomalacia (manifested as bone pain and infrequently contributing to fractures)[2,4], myopathy[2] |
| Frequency Unknown | Arthralgia, myalgia myopathy | | |
| ***Renal and urinary disorders:*** | | | |
| Less frequent | | | increased creatinine, proteinuria, proximal renal tubulopathy including Fanconi syndrome renal failure (acute and chronic), acute tubular necrosis, nephritis (including acute interstitial nephritis)[4], nephrogenic diabetes insipidus |
| Frequency unknown | | | polyuria, renal insufficiency |
| ***Reproductive system and breast disorders:*** | | | |
| Less frequent | gynaecomastia | | |
| ***General disorders and administration site conditions:*** | | | |
| Frequent | fatigue | pain, asthenia, fatigue | asthenia, fatigue |
| Frequency Unknown | asthenia | | |

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

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

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

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

**Description of selected adverse reactions**

*Rash:*

In studies of efavirenz, rashes were usually mild-to-moderate maculopapular skin eruptions that occurred within the first two weeks of initiating therapy with efavirenz. In most patients rash resolved with continuing therapy with efavirenz within one month. TRIOVIR can be

reinitiated in patients interrupting therapy because of rash. Use of appropriate antihistamines and/or corticosteroids is recommended when TRIOVIR is restarted.

*Psychiatric symptoms:*

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

*Nervous system symptoms:*

Nervous system symptoms are common with efavirenz, one of the components of TRIOVIR. In studies of efavirenz, nervous system symptoms of

moderate to severe intensity were experienced by 19% (severe 2%) of patients, and 2% of patients discontinued therapy due to such symptoms. They usually begin during the first one or two days of efavirenz therapy and generally resolve after the first two to four weeks. They may occur more frequently when TRIOVIR is taken concomitantly with meals possibly due to increased efavirenz plasma levels (*see section 5.2*). Dosing at bedtime seems to improve the tolerability of these symptoms (*see section 4.2)*.

*Hepatic failure with efavirenz:*

Hepatic failure, including cases in patients with no pre-existing hepatic disease or other identifiable risk factors, as reported post-marketing, were sometimes characterised by a fulminant course, progressing in some cases to transplantation or death.

*Renal impairment:*

As TRIOVIR may cause renal damage, monitoring of renal function is recommended (*see sections 4.4 and 4.8 Summary of the safety profile*). Proximal renal tubulopathy generally resolved or improved after tenofovir disoproxil discontinuation. However, in some patients, declines in creatinine clearance did not completely resolve despite tenofovir disoproxil discontinuation.

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

*Interaction with didanosine:*

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

*Metabolic parameters:*

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

*Immune Reconstitution Inflammatory Syndrome:*

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

*Osteonecrosis:*

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

**Paediatric population**

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

**Other special populations**

*Elderly:*

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

*Patients with renal impairment:*

Since tenofovir disoproxil can cause renal toxicity, close monitoring of renal function is recommended in any patient with mild renal impairment treated with TRIOVIR (*see sections 4.2, 4.4 and 5.2*).

*HIV/HBV or HCV co-infected patients:*

The adverse reaction profile of efavirenz, emtricitabine and tenofovir disoproxil in patients co-infected with HIV/HBV or HIV/HCV is similar to that observed in patients infected with HIV without co-infection. However, as would be expected in this patient population, elevations in AST and ALT occurs more frequently than in the general HIV infected population.

*Exacerbations of hepatitis after discontinuation of treatment:*

In HIV infected patients co-infected with HBV, clinical and laboratory evidence of hepatitis may occur after discontinuation of treatment *(see section 4.4*).

*Laboratory abnormalities:*

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

***Reporting of suspected adverse reactions***

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicines. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse 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 should be monitored for evidence of toxicity (*see section 4.8)*, including monitoring of vital signs and observation of the patient's clinical status; standard supportive treatment should then be applied as necessary. Administration of activated charcoal may be used to aid removal of unabsorbed efavirenz. Haemodialysis can remove both emtricitabine and tenofovir disoproxil fumarate (refer to detailed information below) but is unlikely

to significantly remove efavirenz from the blood. It is not known whether emtricitabine or tenofovir can be removed by peritoneal dialysis.

**Efavirenz**:

Patients accidentally taking 600 mg efavirenz twice daily have reported increased nervous system symptoms and experienced involuntary muscle contractions.

**Emtricitabine:**

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:**

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

## 5. PHARMACOLOGICAL PROPERTIES

### *5.1 Pharmacodynamic Properties*

Class of Medicine: Antiviral agents, A.20.2.8

*Mechanism of action*

TRIOVIR is a fixed dose combination tablet containing efavirenz, emtricitabine and tenofovir disoproxil fumarate.

**Efavirenz:**

Efavirenz is a non-nucleoside reverse transcriptase inhibitor of HIV-1. Efavirenz activity is mediated predominantly by non-competitive inhibition of HIV-1 reverse transcriptase (RT). HIV-2 RT and human cellular DNA polymerases α, β, γ, and σ are not inhibited by efavirenz.

**Emtricitabine:**

Emtricitabine, a synthetic nucleoside analogue of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5' triphosphate inhibits the activity of the HIV-

1 RT by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine 5'-triphosphate is a weak inhibitor of mammalian DNA polymerase α, β, ε- and mitochondrial DNA polymerase γ.

**Tenofovir disoproxil fumarate:**

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

*Antiviral Activity*

**Efavirenz, emtricitabine and tenofovir disoproxil fumarate:**

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

*Resistance*

**Efavirenz, emtricitabine, and tenofovir disoproxil fumarate:**

HIV-1 isolates with reduced susceptibility to the combination of emtricitabine and tenofovir have been selected in cell culture and in clinical studies. Genotypic analysis of these isolates identified the M184V/I and/or K65R amino acid substitutions in the viral RT. In a clinical study of treatment-naive patients, resistance analysis was performed on HIV isolates from all virologic failure patients with more than 400 copies/ml of HIV-1 RNA at Week 48 or early discontinuations. Genotypic resistance to efavirenz, predominantly the K103N substitution, was the most common form of resistance that developed. Development of efavirenz resistance –associated mutations occurred most frequently and was similar between the treatment arms.

The M184V amino acid substitution, associated with resistance to emtricitabine and lamivudine, was observed in 2/12 (17 %) analysed patient isolates in the emtricitabine + tenofovir disoproxil fumarate group and in 7/22 (32 %) analysed patient isolates in the zidovudine/lamivudine group. Through 48 weeks, no patients developed a detectable K65R mutation in their HIV as analysed through standard genotypic analysis. Insufficient data are available to assess the development of K65R mutation upon prolonged exposure to this regimen.

In treatment-naive patients, isolates from 8 to 47 patients receiving tenofovir disoproxil fumarate developed the K65R substitution through 144 weeks of therapy; 7 of these occurred in the first 48 weeks of treatment and one at week 96. In treatment experienced patients, 14/304 (5 %) of tenofovir disoproxil fumarate treated patients with virologic failure through week 96 showed more than 1,4-fold (median 2,7) reduced susceptibility to tenofovir, Genotypic analysis of the resistant isolates showed a mutation in the HIV-1 RT gene resulting in the K65R amino acid substitution.

**Efavirenz:**

Clinical isolates with reduced susceptibility in cell culture to efavirenz have been obtained. The most frequently observed amino acid substitution in clinical studies with efavirenz is K103N (54 %). One or more RT substitutions at amino acid positions 98, 100, 101, 103, 106, 108, 188, 190, 225, 227 and 230 were observed in patients failing treatment with efavirenz in combination with other anti-retrovirals. Other resistance mutations observed to emerge commonly included L100I (7 %), K101E/Q/R (14 %), V108I (11 %), G190S/T/A (7 %), P225H (18 %) and M230I/L (11 %).

HIV-1 isolates with reduced susceptibility to efavirenz (more than 380-fold increase in $EC_{90}$ value) emerged rapidly under selection in cell culture. Genotypic characterisation of these viruses identified mutations resulting in single amino acid substitutions L100I or V179D, double substitutions L100I/V108I and triple substitutions L100I/V179D/Y181C in RT.

**Tenofovir disoproxil fumarate:**

HIV-1 isolates with reduced susceptibility to tenofovir have been selected in cell culture. These viruses expressed a K65R mutation in RT and showed a 2 to 4-fold reduction in susceptibility to tenofovir.

**Emtricitabine:**

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

**Cross Resistance**

**Efavirenz, emtricitabine and tenofovir disoproxil fumarate:**

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

**Efavirenz:**

Clinical isolates previously characterised as efavirenz-resistant were also phenotypically resistant in cell culture to delavirdine and nevirapine compared to baseline. Delavirdine – and/or nevirapine-resistant clinical viral isolates with NNRTI resistance-associated substitutions (A98G, L100I, K101E/P, K103N/S, V106A, Y181X, Y188X, G190X, P225H, F227L OR M230L) showed reduced susceptibility to efavirenz in cell culture. Greater than 90 % of NRTI-resistant isolates tested in cell culture retained susceptibility to efavirenz.

**Emtricitabine:**

Emtricitabine-resistant isolates (M184V/I) were cross resistant to lamivudine and zalcitabine but retained susceptibility in cell culture to didanosine, stavudine, tenofovir, zidovudine and NNRTIs (delavirdine, efavirenz, and nevirapine). HIV-1 isolates containing K65R substitution, selected in vivo by abacavir, didanosine, tenofovir and zalcitabine demonstrated reduced susceptibility to inhibition by emtricitabine. Viruses harbouring mutations conferring reduced susceptibility to stavudine and zidovudine (M41L, D67N, K70R, L210W, T215Y/F and K219Q/E) or didanosine (L74V) remained sensitive to emtricitabine.

**Tenofovir disoproxil fumarate:**

The K65R mutation selected by tenofovir is also selected in some HIV-1 infected patients treated with abacavir, didanosine or zalcitabine. HIV-1 isolates with the K65R mutation also showed reduced susceptibility to emtricitabine and lamivudine. Therefore, cross-resistance among these medicines may occur in patients whose virus harbours the K65R mutation. HIV-1 isolates from patients whose HIV-1 expressed a mean of 3 zidovudine-associated RT amino acid substitutions (M41L, D67N, K70R, L210W, T215Y/F or K219Q/E/N) showed a 3,1-fold decrease in the susceptibility to tenofovir. Multi-nucleoside resistant HIV-1 with a T69S double insertion mutation in the RT showed reduced susceptibility to tenofovir.

*Paediatric population*

The safety and efficacy of TRIOVIR in children under the age of 18 years have not been established.

***5.2 Pharmacokinetic Properties***

One TRIOVIR tablet is bioequivalent to one 600 mg efavirenz, plus 200 mg emtricitabine plus 300 mg tenofovir disoproxil fumarate following single-dose administration to fasting health subjects.

**Efavirenz:**

In HIV-infected patients time- to- peak plasma concentrations are approximately 3 to 5 hours and steady-state plasma concentrations are reached in 6 to 10 days. It was reported that in 35 patients receiving efavirenz 600 mg once daily, steady state $C_{max}$ was 12,9 ± 3,7 µM (mean ± SD), $C_{max}$ was 5,6 ± 3,2 µM, and AUC was 184 ± 73 µM·hr. Efavirenz is highly bound (approximately 99,5 to 99,75 %) to human plasma proteins, predominantly albumin. Following administration of $^{14}C$-labelled efavirenz, 14 to 34 % of the dose was recovered in the urine (mostly as metabolites) and 16 to 61 % was recovered in faeces (mostly as parent medicine). *In vitro* studies suggest CYP3A4 are the major isozymes responsible for efavirenz metabolism. Efavirenz has been shown to induce P450 enzymes, resulting in induction of its own metabolism. Efavirenz has a terminal half-life of 52 to 76 hours after single doses and 40 to 55 hours after multiple doses.

**Emtricitabine:**

Following oral administration, emtricitabine is well absorbed with peak plasma concentrations occurring at 1 to 2 hours post-dose. Following multiple dose oral administration of emtricitabine to 20 HIV-infected subjects, the steady-state plasma emtricitabine $C_{max}$ was 1,8 ± 0,7 µg/ml (mean ± SD) and the AUC over a 24-hour dosing interval was 10,0 ± 3,1 µg·hr/ml. The mean steady state plasma trough concentration at 24 hours post-dose was 0,09 µg/ml. The mean absolute bioavailability of emtricitabine was 93 %. *In vitro* binding of emtricitabine to human plasma proteins is less than 4 % and is independent of concentration over the range of 0,02 to 200 µg/ml. Following administration of radio-labelled emtricitabine, approximately 86 % is recovered in the urine and 13 % is recovered as metabolites. The metabolites of emtricitabine include 3'-sulfoxidediastereomers and their glucuronic acid conjugate. Emtricitabine is eliminated by a combination of glomerular filtration and active tubular secretion with a renal clearance in adults with normal renal function of 213 ± 89 ml/min (mean ± SD). Following a single oral dose, the plasma emtricitabine half-life is approximately 10 hours.

**Tenofovir disoproxil fumarate:**

Following oral administration of a single 300 mg dose of tenofovir disoproxil fumarate to HIV-1 infected patients in the fastest state, maximum serum concentrations ($C_{max}$) were achieved in 1,0 ± 0,4 hours (mean ± SD) and $C_{max}$ and AUC values were 296 ± 90 ng/ml and 2 287 ± 685 ng·hr/ml, respectively. The oral bioavailability of tenofovir from tenofovir disoproxil fumarate in fasted patients is approximately 25 %. *In vitro* binding of tenofovir to human plasma proteins is less than 0,7 % and is independent of concentration over the range of 0,01 to 25 µg/ml. Approximately 70 to 80 % of the intravenous dose of tenofovir is recovered as unchanged medicine in the urine. 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, the terminal elimination half-life of tenofovir is approximately 17 hours.

*Absorption*

In HIV infected patients, peak efavirenz plasma concentrations were attained by 5 hours and steady-state concentrations reached in 6 to 7 days.

Emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1 to 2 hours post-dose.

Following oral administration of a single 300 mg dose of tenofovir disoproxil to HIV-1 infected patients in the fasted state, maximum tenofovir concentrations were achieved within one hour. The oral bioavailability of tenofovir from tenofovir disoproxil in fasted patients was approximately 25%.

***Effects of Food on Oral Absorption***

TRIOVIR has not been evaluated in the presence of food. Administration of efavirenz tablets with a high fat meal increased the mean AUC and $C_{max}$ of efavirenz by 28 % and 79 %, respectively, compared to administration in the 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 (*see sections 4.9 and 4.8 and 4.4*).

***Distribution***

Efavirenz is highly bound (> 99 %) to human plasma proteins, predominantly albumin.

*In vitro* binding of emtricitabine to human plasma proteins is < 4 % and independent of concentrations over the range of 0.02 to 200 µg/ml. Following intravenous administration, the volume of distribution of emtricitabine was approximately 1.4 l/kg. After oral administration, emtricitabine is widely distributed throughout the body. The mean plasma to blood concentration ratio is approximately 1.0 and the mean semen to plasma concentration ratio was approximately 4.0.

*In vitro* binding of tenofovir to human plasma or serum protein is < 0.7 % and 7.2 %, respectively over the tenofovir concentration range 0.01 to 25 µg/ml. Following intravenous administration, the volume of distribution of tenofovir was approximately 800 ml/kg. After oral administration, tenofovir is widely distributed throughout the body.

***Biotransformation***

Studies in humans and *in vitro* studies using human liver microsomes have demonstrated that efavirenz is principally metabolised by the CYP system to hydroxylated metabolites with

subsequent glucuronidation of these hydroxylated metabolites. These metabolites are essentially inactive against HIV-1.

The *in vitro* studies suggest that CYP3A4 and CYP2B6 are the major isozymes responsible for efavirenz metabolism and that it inhibits CYP isozymes 2C9, 2C19, and 3A4.

In *in vitro* studies efavirenz did not inhibit CYP2E1 and inhibited CYP2D6 and CYP1A2 only at concentrations well above those achieved clinically.

Efavirenz plasma exposure may be increased in patients with homozygous G516T genetic variant of the CYP2B6 isozyme. The clinical implications of such an association are unknown; however, the potential for an increased frequency and severity of efavirenz-associated adverse events cannot be excluded.

Efavirenz has been shown to induce CYP3A4 and CYP2B6, resulting in the induction of its own metabolism, which may be clinically relevant in some patients. In uninfected volunteers, multiple doses of 200 to 400 mg per day for 10 days resulted in a lower than predicted extent of accumulation (22 to 42 % lower) and a shorter terminal half-life of 40 to 55 hours (single dose half-life 52 to 76 hours). Efavirenz has also been shown to induce UGT1A1. Exposures of raltegravir (a UGT1A1 substrate) are reduced in the presence of efavirenz.

Although *in vitro* data suggest that efavirenz inhibits CYP2C9 and CYP2C19, there have been contradictory reports of both increased and decreased exposures to substrates of these enzymes when co-administered with efavirenz *in vivo*. The net effect of co-administration is not clear.

There is limited metabolism of emtricitabine. The biotransformation of emtricitabine includes oxidation of the thiol moiety to form the 3'-sulphoxide diastereomers (approximately 9 % of dose) and conjugation with glucuronic acid to form 2'-O-glucuronide (approximately 4 % of dose).

*In vitro* studies have determined that neither tenofovir disoproxil nor tenofovir are substrates for the CYP enzymes. Neither emtricitabine nor tenofovir inhibited *in vitro* drug metabolism mediated by any of the major human CYP isoforms involved in drug biotransformation. Also, emtricitabine did not inhibit uridine 5'-diphosphoglucuronyl transferase, the enzyme responsible for glucuronidation.

***Elimination***

Efavirenz has a relatively long terminal half-life of at least 52 hours after single doses and 40 to 55 hours after multiple doses. Approximately 14 to 34 % of a radiolabelled dose of efavirenz is recovered in the urine and less than 1 % of the dose was excreted in urine as unchanged efavirenz. Following oral administration, the elimination half-life of emtricitabine is approximately 10 hours. Emtricitabine is primarily excreted by the kidneys with complete recovery of the dose achieved in urine (approximately 86 %) and faeces (approximately 14 %). Thirteen percent of the emtricitabine dose was recovered in urine as three metabolites. The systemic clearance of emtricitabine averaged 307 ml/min.

Following oral administration, the elimination half-life of tenofovir is approximately 12 to 18 hours. Tenofovir is primarily excreted by the kidneys by both filtration and an active tubular transport system with approximately 70 to 80 % of the dose excreted unchanged in urine following intravenous administration. The apparent clearance of tenofovir averaged approximately 307 ml/min. Renal clearance is 210 ml/min, which is in excess of the glomerular filtration rate. This indicates that active tubular secretion is an important part of the elimination of tenofovir

**c. Characteristics in specific groups of patients**.

***Age***

Pharmacokinetic studies have not been evaluated with efavirenz, emtricitabine or tenofovir in elderly patients (over 65 years of age) (*see sections 4.4 and 4.8*).

***Gender***

The pharmacokinetics of emtricitabine and tenofovir are similar in male and female patients. Limited data suggest that females may have higher exposure to efavirenz, but they do not appear to be less tolerant of efavirenz.

***Ethnicity***

Efavirenz: the pharmacokinetics of efavirenz in patients appear to be similar among the racial groups studied

Limited data suggest that Asian and Pacific Island patients may have higher exposure to efavirenz but they do not appear to be less tolerant of efavirenz.

**Emtricitabine:**

No pharmacokinetic differences due to race have been identified following the administration of emtricitabine.

**Tenofovir disoproxil fumarate:**

There were insufficient numbers from racial and ethnic groups other than Caucasian to adequately determine potential pharmacokinetic differences among these populations following the administration of tenofovir disoproxil fumarate.

**Paediatric population**

Pharmacokinetic studies have not been performed with tenovir disoproxil fumarate in infants and children under 18 years of age (*see section 4.2*). Efavirenz has not been studied in paediatric patients below 3 years of age or who weigh less than 13 kg. Emtricitabine has been studied in paediatric patients from 3 months to 17 years of age. TRIOVIR is not recommended for paediatric administration.

**Patients with Impaired Renal Function**

The pharmacokinetics of efavirenz, emtricitabine and tenofovir disoproxil after co-administration of the separate pharmaceutical forms or as fixed dose combination have not been studied in HIV infected patients with renal impairment.

**Efavirenz:**

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

**Emtricitabine and tenofovir disoproxil fumarate:**

The pharmacokinetics of emtricitabine and tenofovir disoproxil fumarate are altered in patients with renal impairment. In patients with creatinine clearance less than 50 ml/min, $C_{max}$ and $AUC_{0-\infty}$ of emtricitabine and tenofovir were increased *(see sections 4.3 and 4.4)*.

**Patients with Hepatic Impairment**

**Efavirenz:**

The pharmacokinetics of efavirenz have not been adequately studied in patients with hepatic impairment *(see sections 4.4 and 4.8).*

**Emtricitabine:**

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

**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.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Core:

Microcrystalline cellulose,

Croscarmellose sodium,

Hydroxypropyl cellulose,

Sodium lauryl sulphate,

Purified water,

Lactose monohydrate,

Magnesium stearate,

Polyvinyl alcohol.

Coating:

Titanium dioxide,

macrogol,

talc,

iron oxide red,

iron oxide black.

OR

Polyvinyl alcohol,

Macrogol/PEG,

Talc,

Titanium dioxide,

Iron oxide red,

Iron oxide black.

### 6.2 Incompatibilities

None

### 6.3 Shelf Life

3 years

### 6.4 Special precautions for storage

TRIOVIR tablets should be stored at or below 30 °C.

The bottle should be kept tightly closed and the silica gel sachet should not be removed from the bottle after opening.

Protect from moisture and keep well closed.

### 6.5 Nature and contents of container

TRIOVIR 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, packed in an outer carton in 28's and 30's.

TRIOVIR 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 without outer carton in pack sizes of 28's and 30's.

TRIOVIR 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 along with wad containing aluminium induction sealing liner with desiccant sieve sachet, packed in an outer carton in 90's.

TRIOVIR 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, packed in an outer carton in 28's and 30's.

TRIOVIR 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 without outer carton, packed in 28's and 30's.

TRIOVIR is packed in high density polypropylene (HDPE) bottle pack comprising of white opaque wide mouth HDPE bottle with a white opaque polypropylene screw closure along with wad containing aluminium induction sealing liner with desiccant sieve sachet packed without carton, packed in 84's.

### 6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be returned to the pharmacy for destruction or it must be disposed of in accordance with local requirements for medical waste destruction.

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

Viatris Healthcare (Pty) Ltd

4 Brewery Street

Isando

Republic of South Africa

## 8. REGISTRATION NUMBERS

52/20.2.8/0062

## 9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

4 May 2021

## 10. DATE OF REVISION OF TEXT

4 July 2023