PROFESSIONAL INFORMATION FOR TRIVAGE TABLETS

SCHEDULING STATUS: **S4**

PROPRIETARY NAME (AND DOSAGE FORM):

TRIVAGE TABLETS (Film-coated Tablets)

COMPOSITION:

Each film-coated tablet contains efavirenz 600 mg, emtricitabine 200 mg, tenofovir disoproxil fumarate 300 mg. Sugar free.

Other ingredients include microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, sodium lauryl sulfate, magnesium stearate (vegetable grade), pregelatinised starch, polyvinyl alcohol, titanium dioxide (C.I. No. 77891), polyethylene glycol, talc, red iron oxide (C.I. No. 77491), black iron oxide (C.I. No. 77499).

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.8 Antimicrobial (chemotherapeutic) agents. Antiviral agents.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

TRIVAGE TABLETS is a fixed dose combination tablet containing efavirenz, emtricitabine and tenofovir disoproxil fumarate (tenofovir DF). Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI); emtricitabine is a synthetic nucleoside analogue of cytidine and tenofovir DF is converted *in vivo* to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analogue of adenosine 5' monophosphate.

Efavirenz:

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

Emtricitabine:

Emtricitabine, a nucleoside reverse transcriptase inhibitor (NRTI), is a synthetic nucleoside analogue of cytidine. Cellular enzymes phosphorylate emtricitabine to emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate competes with the natural substrate, deoxycytidine 5'-triphosphateand is incorporated into nascent viral DNA leading to chain termination. Emtricitabine 5'-triphosphate weakly inhibits mammalian DNA polymerase α, β, ε and mitochondrial DNA polymerase γ.

Tenofovir disoproxilfumarate:

Tenofovir DF, a NRTI, is an acyclic nucleoside phosphonate diester analogue of adenosine monophosphate and 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 through competing with the natural substrate deoxyadenosine 5'-triphosphate. After incorporation into DNA, the DNA chain is terminated. Tenofovir diphosphate weakly inhibits mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Antiviral activity:

Efavirenz, emtricitabine and tenofovir disoproxil fumarate:

In combination studies that evaluated the antiviral activity *in vitro* 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 demonstrating reduced susceptibility to the emtricitabine and tenofovir combination have been selected *in vitro*.

Following genotypic analysis, the M184V/I and/or K65R amino acid substitutions were identified in the viral RT.

Efavirenz:

Clinical isolates with reduced susceptibility *in vitro* 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

antiretrovirals. 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 EC90 value) emerged rapidly under selection *in vitro*. 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.

Emtricitabine:

HIV isolates resistant to emtricitabine have been selected *in vitro*. Genotypic analysis of these isolates demonstrated that reduced emtricitabine susceptibility was associated with a mutation in the HIV RT gene at codon 184. This mutation caused an amino acid substitution of methionine by valine or isoleucine (M184V/I).

Tenofovir disoproxil fumarate:

Isolates of HIV-1 that exhibited reduced susceptibility to tenofovir have been selected *in vitro*. These viruses expressed a K65R mutation in reverse transcriptase and demonstrated a reduced susceptibility to tenofovir of between 2- and 4-fold.

Cross-resistance:

Efavirenz, emtricitabine and tenofovir disoproxil fumarate:

Cross-resistance has been recognised among NNRTIs. It is also known that cross-resistance may develop among certain NRTIs. The M184V/I and/or K65R substitutions selected *in vitro* by the combination of emtricitabine and tenofovir are also seen in some HIV-1 strains isolated from individuals failing treatment with tenofovir in combination with either lamivudine or emtricitabine, and either abacavir or didanosine. Cross-resistance among these medicines may therefore develop in patients whose virus harbours either or both of these amino acid substitutions.

Pharmacokinetic properties:

Efavirenz:

Absorption:

Peak efavirenz plasma concentrations of 1,6 – 9,1 µM are reached by 5 hours following single oral doses of 100 mg to 1600 mg given to uninfected volunteers. Although dose-related increases in C_{max} and AUC are seen for doses up to 1600 mg, these increases are less than proportional, indicating

diminished absorption at higher doses. Steady state plasma concentrations are reached in 6 to 10 days.

Distribution:

Efavirenz is highly plasma protein bound (approximately 99,5 – 99,75 %) and predominantly to albumin. Cerebrospinal fluid concentrations ranged from 0,26 to 1,19 % (mean 0,69 %) of the corresponding plasma concentrations in HIV-1 infected individuals administered 200 to 600 mg efavirenz once daily for at least one month. This is about three times higher than the non-protein-bound (free) fraction of efavirenz in plasma.

Metabolism:

Efavirenz is principally metabolised by the cytochrome P450 system to hydroxylated metabolites with subsequent glucuronidation of these hydroxylated metabolites. The metabolites are not active against HIV-1. CYP3A4 and CYP2B6 are the major isozymes involved in efavirenz metabolism. Efavirenz, through induction of P450 enzymes, induces its own metabolism.

Elimination:

Efavirenz has a long terminal half-life of 52 – 76 hours and 40 – 55 hours after single and multiple doses, respectively. Subsequent to the administration of a radio-labelled dose, 14 – 34 % of efavirenz is recovered in the urine (mostly as metabolites) and 16 – 61 % is recovered in the faeces (mostly as parent medicine).

Emtricitabine:

The pharmacokinetic properties of emtricitabine are summarised in Table 1.

Absorption: Following oral administration of emtricitabine (200 mg), emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1 – 2 hours post-dose. *Distribution:In vitro* binding of emtricitabine to human plasma proteins is < 4 % and is independent of concentration over the range of 0,02 – 200 µg/mℓ.

Metabolism and elimination: 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'-sulfoxide diastereomers and their glucuronic acid conjugate. Emtricitabine is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of emtricitabine (200 mg), the plasma emtricitabine half-life is approximately 10 hours.

Tenofovir Disoproxil Fumarate:

The pharmacokinetic properties of tenofovir disoproxil fumarate are summarised in Table 1.

Absorption: Following oral administration of tenofovir, maximum tenofovir serum concentrations are achieved in 1,0 ± 0,4 hour.

Distribution: *In vitro* binding of tenofovir to human plasma proteins < 0,7 % is independent of concentration over the range of 0,01 – 25 µg/mℓ.

Metabolism and elimination: Approximately 70 – 80 % of the intravenous dose of tenofovir is recovered as unchanged in the urine. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of tenofovir, the terminal elimination half-life of tenofovir is approximately 17 hours.

Table 1: Single Dose Pharmacokinetic Parameters for Emtricitabine and Tenofovir in Adults

	Emtricitabine	**Tenofovir**
Fasted Oral Bioavailability[2] (%)	92 (83,1 – 106,4)	25 (NC[1] – 45,0)
Plasma Terminal Elimination Half-Life[2] (hr)	10 (7,4 – 18,0)	17 (12,0 – 25,7)
C_{max}[3] (µg/mℓ)	1,8 ± 0,72[4]	0,30 ± 0,09
AUC[3] (µg•hr/mℓ)	10,0 ± 3,12[4]	2,29 ± 0,69
CL/F[3](mℓ/min)	302 ± 94	1043 ± 115
CL_{renal}[3] (mℓ/min)	213 ± 89	243 ± 33

[1] NC = Not calculated

[2] Median (range)

[3] Mean (± SD)

[4] Data presented as steady state values.

Effects of food on oral absorption:

TRIVAGE TABLETS 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 DF 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 weigh less than 13 kg. Emtricitabine has been studied in paediatric patients from 3 months to 17 years of age. **TRIVAGE TABLETS** is not recommended for paediatric administration. Pharmacokinetics of efavirenz, emtricitabine, and tenofovir have not been fully evaluated in the elderly (more than 65 years) (see **WARNINGS AND SPECIAL PRECAUTIONS**).

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 impact of renal impairment on efavirenz elimination should be minimal.

Emtricitabine and tenofovir disoproxil fumarate: The pharmacokinetics of emtricitabine and tenofovir DF 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 **CONTRAINDICATIONS, WARNINGS AND SPECIAL PRECAUTIONS, Renal impairment**).

Patients with hepatic impairment

Efavirenz: The pharmacokinetics of efavirenz have not been adequately studied in patients with hepatic impairment (see **WARNINGS AND SPECIALPRECAUTIONS**).

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 limited.

Tenofovir disoproxil fumarate: The pharmacokinetics of tenofovir following a 300 mg dose of tenofovir DF 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.

INDICATIONS:

TRIVAGE TABLETS is indicated as mono- or combination therapy with other anti-retroviral medicines for HIV-1 infection in adults.

CONTRAINDICATIONS:

TRIVAGE TABLETS is contraindicated in patients:

- With previously demonstrated hypersensitivity to efavirenz, emtricitabine or tenofovir or to any of the other components of **TRIVAGE TABLETS**.
- Severe hepatic impairment (Child Pugh Class C).
- A history of previous liver injury/failure with efavirenz containing antiretroviral treatment (ART).
- With moderate to severe impairment of renal function (creatine clearance < 50 mℓ) (see **WARNINGS AND SPECIAL PRECAUTIONS** and **DOSAGE AND DIRECTIONS FOR USE**).
- Who are concurrently receiving treatment with cisapride, midazolam, triazolam, pimozide, bepridil or ergot alkaloids (for example ergotamine, dihydroergotamine, ergonovine and methylergonovine), because competition for CYP3A4 by the efavirenz in **TRIVAGE TABLETS** could result in inhibition of the metabolism of these medicines and create the potential for serious and/or life-threatening adverse events (e.g., cardiac dysrhythmias, prolonged sedation or respiratory depression).
- Who are concurrently using voriconazole, since efavirenz significantly decreases voriconazole plasma concentrations, while voriconazole significantly increases efavirenz plasma concentrations. (See **INTERACTIONS**). Since **TRIVAGE TABLETS** is a fixed-dose combination medicine, the dose of efavirenz cannot be altered; therefore voriconazole and **TRIVAGE TABLETS** must not be co-administered.
- Who are pregnant or breastfeeding (see **PREGNANCY AND LACTATION**).

- Who are concurrently using St. John's Wort (*Hypericum perforatum*) or St. John's Wort containing medicines (see **INTERACTIONS**).
- **TRIVAGE TABLETS** is not recommended for use in children and adolescents below 18 years of age due to lack of data on safety and efficacy.

WARNINGS AND SPECIAL PRECAUTIONS:

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 ANTI-RETROVIRALS.

TRIVAGE TABLETS ARE NOT INDICATED FOR THE TREATMENT OF CHRONIC HBV INFECTION AND SAFETY AND EFFICACY OF **TRIVAGE TABLETS** HAVE NOT BEEN ESTABLISHED IN PATIENTS CO-INFECTED WITH HBV AND HIV. SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO HAVE DISCONTINUED EMTRICITABINE OR TENOFOVIR DF. IN SOME OF THESE PATIENTS TREATED WITH EMTRICITABINE, THE EXACERBATION OF HEPATITIS B WERE ASSOCIATED WITH LIVER DECOMPENSATION AND LIVER FAILURE. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS CO-INFECTED WITH HIV AND HBV WHO HAVE DISCONTINUED **TRIVAGE TABLETS**. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED.

Lactic acidosis / hyperlactataemia:

Use of **TRIVAGE TABLETS** 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, 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 medicines that are less likely to cause lactic acidosis.

- **Lactate 5 – 10 mmol/ℓ with symptoms and or with reduced 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 **TRIVAGE TABLETS** to patients with known factors for liver disease.

Treatment with **TRIVAGE TABLETS** should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatoxicity.

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 signs or symptoms.

Pancreatitis:

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

Liver disease:

Use of **TRIVAGE TABLETS** can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of **TRIVAGE TABLETS** 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 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/µl and female gender.

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

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

Liver enzymes:

Monitoring of liver enzyme levels is recommended in patients with known or suspected history of hepatitis B or C infection and in patients treated with other medicines associated with hepatic toxicity. The benefit of continued therapy with **TRIVAGE TABLETS** has to be weighed against the unknown risks of significant hepatic toxicity in patients who show persistent elevations of serum transaminases to greater than 5 times the upper limit of the normal range (see **Side Effects**).

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

Patients with HIV and hepatitis B or C virus co-infection:

It is recommended that all patients with HIV be tested for the presence of chronic HBV before initiating anti-retroviral therapy. **TRIVAGE TABLETS** are not indicated for the treatment of chronic HBV infection and safety and efficacy of **TRIVAGE TABLETS** have not been established in patients co-infected with HBV and HIV. Severe acute exacerbations of hepatitis B have been reported in patients co-infected with HBV and HIV and who have discontinued emtricitabine or tenofovir DF. In some of these patients treated with emtricitabine, the exacerbation of hepatitis B were associated with liver decompensation and liver failure. Hepatic function should be monitored closely with both clinical and laboratory follow up for at least several months in patients co-infected with HBV and HIV and who have discontinued **TRIVAGE TABLETS**. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

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.

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 **TRIVAGE TABLETS**therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis.

Co-administration with related medicines:

Related medicines not for co-administration with **TRIVAGE TABLETS** include emtricitabine, tenofovir DF, emtricitabine/tenofovir DF and efavirenz which contain the same active components

as **TRIVAGE TABLETS**. Due to similarities between emtricitabine and lamivudine, **TRIVAGE TABLETS** should not be co-administered with medicines containing lamivudine, including lamivudine/zidovudine, lamivudine, and abacavir.

St. John's Wort:

Concomitant use of **TRIVAGE TABLETS** and St. John's Wort (*Hypericum perforatum*) or St. John's Wort containing products is contraindicated. 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.

Psychiatric symptoms:

Serious psychiatric adverse events have been reported in patients treated with efavirenz. These side effects include: severe depression, suicidal ideation, nonfatal suicide attempts, aggressive behaviour, paranoid reactions and manic reactions. Treatment with efavirenz is associated with an increase in the occurrence of these psychiatric symptoms.

There have also been post marketing reports of death by suicide, delusions, and psychosis-like behaviour; a causal relationship to the use of efavirenz cannot be determined from these reports. Patients with serious psychiatric adverse experiences should seek immediate medical evaluation to assess the possibility that the symptoms may be related to the use of efavirenz, therefore **TRIVAGE TABLETS**.

Nervous system and psychiatric symptoms:

These symptoms included dizziness, insomnia, impaired concentration, somnolence, abnormal dreams and hallucinations. Other reported symptoms are euphoria, confusion, agitation, amnesia, stupor, abnormal thinking, and depersonalisation. These symptoms usually begin during the first or second day of therapy and may resolve after the first 2 - 4 weeks of therapy. Patients should be informed that these common symptoms may improve with continued therapy and may not be predictive of subsequent onset of the less frequent psychiatric symptoms. Dosing at bedtime may improve the tolerability of these nervous system symptoms.

Patients receiving **TRIVAGE TABLETS**should be alerted to the potential for additive central nervous system effects when **TRIVAGE TABLETS** is used concomitantly with alcohol or psychoactive medicines.

Renal impairment:

Emtricitabine and tenofovir, two of the active ingredients in **TRIVAGE TABLETS**, are principally eliminated by the kidney. **TRIVAGE TABLETS** should not be administered to patients with creatinine clearance < 50 mℓ/min (see **Contraindications**).

There have been reports of renal impairment including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphataemia) in association with the use of tenofovir DF (see **Side Effects**).

It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with **TRIVAGE TABLETS** (see **Dosage and Directions for Use**). Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment.

The use of **TRIVAGE TABLETS** should be avoided in patients who are concurrently taking or who have recently taken a nephrotoxicmedicine.

Skin rash:

Mild-to-moderate rash, which may resolve with continued treatment, has been observed with efavirenz use. Treatment with appropriate antihistamines and/or corticosteroids may improve tolerability and hasten resolution of symptoms. Treatment with **TRIVAGE TABLETS** should be discontinued in patients who experience severe rash associated with blistering, desquamation, mucosal involvement or fever (see **Side effects**).

Cholesterol:

Monitoring of cholesterol and triglyceride levels should be considered in patients treated with **TRIVAGE TABLETS** (see **Side Effects**).

***Bone effects*:**

TRIVAGE TABLETS decreases bone mineral density. 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.

Osteonecrosis:

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported, particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (cART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Convulsions:

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 phenobarbitone, may require periodic monitoring of plasma levels (see **INTERACTIONS**).

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.

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 it 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.

Opportunistic infections:

Patients receiving **TRIVAGE TABLETS**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 **TRIVAGE TABLETS**, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Paediatric and adolescent use:

The safety and efficacy of **TRIVAGE TABLETS**in children and adolescents less than 18 years of age have not been established, therefore **TRIVAGE TABLETS** is not recommended in this age group.

Use in the elderly:

Clinical studies of fixed dose combinations of emtricitabine and tenofovir, as in **TRIVAGE TABLETS**, did not include sufficient numbers of individuals older than 65 years to establish whether they respond differently from younger subjects. Generally, caution is required when doses are selected for elderly patients, bearing in mind the greater frequency of decreased liver, kidney and cardiac function, and of concomitant disease or therapy with other medicines.

Effects on the ability to drive and use machines:

TRIVAGE TABLETSmay lead to dizziness, impaired concentration, and/or drowsiness. Patients should be instructed that, if they develop these symptoms, they should keep away from potentially hazardous tasks, such as driving or operating machinery.

INTERACTIONS:

Efavirenz: Efavirenz has been shown *invivo* to induce CYP3A4 and CYP2B6. Other compounds that are substrates of CYP3A4 may have decreased plasma concentrations when co-administered with efavirenz. *In vitro* studies have demonstrated that efavirenz inhibits 2C9 and 2C19 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 that induce CYP3A4 activity (e.g., phenobarbitone, rifampicin, rifabutin) would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations. Efavirenz exposure may be increased by medicines (such as ritonavir) or grapefruit juice which inhibit CYP3A4 or CYP2B6 activity.

Emtricitabine and tenofovir disoproxil fumarate: Since emtricitabine and tenofovir are primarily eliminated by the kidneys, co-administration of **TRIVAGE TABLETS** 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, valaciclovir, and valganciclovir, aminoglycosides, amphotericin B, foscarnet, pentamidine and interleukin-2.

Co-administration of tenofovir DF and didanosine should be undertaken with cautionand patients receiving this combination should be monitored closely for didanosine-associatedadverse events. Didanosine should be discontinued in patients who develop didanosine-associated adverse events (for didanosine dosing adjustment recommendations, see Table 3). Suppression of CD4 cell counts has been observed in patients receiving tenofovir DF with didanosine 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 DF should be monitored for tenofovir-associated adverse events. **TRIVAGE TABLETS**should be discontinued in patients who develop tenofovir-associated adverse events (For atazanavir dosing adjustment recommendations see Table 3).

Other important medicine interaction information for **TRIVAGE TABLETS**is summarised in Table 2 and 3. The medicine interactions described are based on studies conducted with efavirenz, emtricitabine or tenofovir DF as individual medicines or are potential medicine interactions; no medicine interaction studies have been conducted using the combination of actives such as in**TRIVAGE TABLETS**. The tables include potentially significant interactions, but are not all inclusive.

Table: 2

Medicines that are contraindicated or not recommended for use with TRIVAGE TABLETS

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.

Anti-migraine: ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine)	CONTRAINDICATED due to potential for serious and/ or life threatening reactions such as acute ergot toxicity characterised by peripheral vasospasm and ischaemia of the extremities and other tissues.
Anti-retroviral: efavirenz, emtricitabine, tenofovir DF, lamivudine	Not for use with **TRIVAGE TABLETS** because the active ingredients- emtricitabine, tenofovir DF, emtricitabine/tenofovir DF and efavirenz are components of **TRIVAGE TABLETS**. 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: bepridil	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.
GI motility medicine: cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.
Neuroleptic: pimozide	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.
St. John's Wort (*Hypericum perforatum*)	CONTRAINDICATED: Expected to substantially decrease plasma levels of efavirenz; has not been studied in combination with efavirenz.

Table: 3

Established and Other Potentially Significant[1] Medicine Interactions:

Alteration in Dose or Regimen May Be Recommended Based onMedicine Interaction Trials or Predicted Interaction

Concomitant Medicine Class: Medicine Name	**Effect**	**Clinical Comment**
Antiretroviral medicines		
Protease inhibitor: Amprenavir	↓ amprenavir concentration	Efavirenz has the potential to decrease serum concentrations of amprenavir.

Protease inhibitor: Fosamprenavir calcium	↓ amprenavir concentration	Fosamprenavir (unboosted): Appropriate doses of fosamprenavir and **TRIVAGE TABLETS** with respect to safety and efficacy have not been established. Fosamprenavir/ritonavir: An additional 100 mg/day (300 mg total) of ritonavir is recommended when **TRIVAGE TABLETS** is administered with fosamprenavir once daily. No change in the ritonavir dose is required when **TRIVAGE TABLETS** is administered with fosamprenavir/ritonavir once daily. No change in the ritonavir dose is required when **TRIVAGE TABLETS** is administered with fosamprenavir plus ritonavir twice daily.
Protease inhibitor: Atazanavir	↓ atazanavir concentration ↑ tenofovir concentration	Plasma concentration of atazanavir was decreased by both efavirenz or tenofovir DF. Sufficient data are not available to make a dosing recommendation for atazanavir or atazanavir/ritonavir with **TRIVAGE TABLETS**. Therefore co-administration of **TRIVAGE TABLETS** and atazanavir is not recommended due to concerns regarding decreased atazanavir concentration.
Protease inhibitor: Indinavir	↓ indinavir concentration.	The optimal dose of indinavir, when given in combination with efavirenz, is not known. Increasing the indinavir dose to 1000 mg every 8 hours does not compensate for the

		increased indinavir metabolism due to efavirenz.
Protease inhibitor: Lopinavir/ritonavir	↓ lopinavir concentration ↑ tenofovir concentration	A dose increase of lopinavir/ritonavir to 600/150 mg (3 tablets) twice daily may be considered when used in combination with efavirenz in treatment- experienced patients where decreased susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). **Patients should be monitored for tenofovir-associated adverse events. TRIVAGE TABLETS should be discontinued in patients who develop tenofovir-associated adverse events.**
Protease inhibitor: Ritonavir	↑ ritonavir concentration ↑ 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). Monitoring of liver enzymes is recommended when **TRIVAGE TABLETS** is used in combination with ritonavir.
Protease Inhibitor: Saquinavir	↑ saquinavir concentration	Should not be used as sole protease inhibitor in combination with **TRIVAGE TABLETS**.
NRTI: Didanosine	↑ didanosine concentration	Higher didanosine concentrations could potentiate didanosine-associated adverse events, including pancreatitis and

		neuropathy. **In adults weighing more than 60 kg, the didanosine dose should be reduced to 250 mg if co-administered with TRIVAGE TABLETS Data are not available to recommend a dose adjustment of didanosine for patients weighing less than 60 kg.** When co-administered, **TRIVAGE TABLETS** and didanosine may be taken under fasted conditions or with a light meal (less than 400 kcal, 20 % fat). Co-administration of didanosine buffered formulation with **TRIVAGE TABLETS** should be under fasted conditions. **Co-administration of TRIVAGE TABLETS and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse events.**
Other medicines		
Anticoagulant: Warfarin	↑ or ↓ warfarin concentration	Plasma concentrations and effects potentially increased or decreased by efavirenz.
Anticonvulsants: Carbamazepine	↓ carbamazepine concentration ↓ efavirenz concentration	There are insufficient data to make a dose recommendation for **TRIVAGE TABLETS**. Alternative anticonvulsant treatment should be used.
Phenytoin Phenobarbitone	↓ anticonvulsant concentration ↓ efavirenz	Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic

	concentration	monitoring of anticonvulsant plasma levels should be conducted.
Valproic acid/Efavirenz	No clinically significant effect on efavirenz pharmacokinetics. Limited data suggest there is no clinically significant effect on valproic acid pharmacokinetics.	**TRIVAGE TABLETS** and valproic acid can be co-administered without dose adjustment. Patients should be monitored for seizure control.
Vigabatrin/Efavirenz Gabapentin/Efavirenz	Interaction not studied. Clinically significant interactions are not expected since vigabatrin and gabapentin are exclusively eliminated unchanged in the urine and are unlikely to compete for the same metabolic enzymes and elimination pathways as efavirenz	**TRIVAGE TABLETS** and vigabatrin or gabapentin can be co-administered without dose adjustment.

Antidepressant : Sertraline.	↓ sertraline concentration	Increases in sertraline dose should be guided by clinical response.
Paroxetine/Efavirenz	Paroxetine: AUC: ↔ $C_{max:}$ ↔ C_{min}: ↔ Efavirenz: AUC: ↔ $C_{max:}$ ↔ C_{min}: ↔	**TRIVAGE TABLETS** and paroxetine can be co-administered without dosage adjustment.
Fluoxetine/Efavirenz	Interaction not studied. Since fluoxetine shares a similar metabolic profile with paroxetine, i.e. a strong CYP2D6 inhibitory effect, a similar lack of interaction would be expected for fluoxetine	**TRIVAGE TABLETS** and fluoxetine can be co-administered without dosage adjustment.
Antifungals: Itraconazole Posaconazole	↓ itraconazole concentration ↓ hydroxy-itraconazole concentration ↓ posaconazole	Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered. Concomitant use should be avoided.

Ketoconazole	↓ ketoconazole concentration	Medicine interaction studies with **TRIVAGE TABLETS** and ketoconazole have not been conducted. Efavirenz has the potential to decrease plasma concentrations of ketoconazole.
Anti-infective: Clarithromycin.	↓ clarithromycin concentration ↑14-OH metabolite concentration	Clinical significance unknown. In uninfected volunteers, 46 % developed rash while receiving efavirenz and clarithromycin. No dose adjustment of **TRIVAGE TABLETS** is recommended when given with clarithromycin. Alternative to clarithromycin such as azithromycin should be considered. Other macrolide antibiotics, such as, erythromycin, have not been studied in combination with **TRIVAGE TABLETS**.
Antimycobacterial: Rifabutin	↓ rifabutin concentration	Increase daily dose of rifabutin by 50 %. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week.
Antimycobacterial: Rifampicin	↓ efavirenz concentration	Clinical significance of reduced Efavirenz concentration is unknown. Dosing recommendations for concomitant use of **TRIVAGE TABLETS** and rifampicin have not been established.
Calcium channel blockers: Diltiazem	↓ diltiazem concentration ↓ desacetyl diltiazem concentration	Diltiazem dose adjustments should be guided by clinical response. No dose adjustment of **TRIVAGE TABLETS** is necessary when administered with diltiazem.

Others (e.g., felodipine, nifedipine, nicardipine, verapamil)	↓ N-monodesmethyl diltiazem concentration ↓ calcium channel blocker.	No data are available on potential interactions of efavirenz with other calcium channel blockers that are substrates of CYP3A4 enzymes. The potential exists for reduction in plasma concentrations of the calcium channel blocker. Dose adjustments should be guided by clinical response.
HMG-CoA reductase inhibitors: Atorvastatin, Pravastatin, Simvastatin	↓ atorvastatin concentration ↓ pravastatin concentration ↓ simvastatin concentration	Plasma concentrations of atorvastatin pravastatin and simvastatin decreased with efavirenz. Consult the full package inserts for the HMG-CoA reductase inhibitor for guidance on individualising the dose.
Narcotic analgesic: Methadone	↓ methadone concentration	Co-administration of efavirenz in HIV-1 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 contraceptives: Ethinyl oestradiol	↑ ethinyl oestradiol concentration	Clinical significance unknown. Because the potential interaction of efavirenz with oral contraceptives has not been fully characterised. A reliable method of barrier

		contraception should be used in addition to oral contraceptives.
Artemether/Lumefantrine/Efavirenz (20/120 mg tablet, 6 doses of 4 tablets each over 3 days/600 mg daily.)	Artemether: AUC: ↓ 51 % C_{max}: ↓ 21 % Dihydroartemisinin (active metabolite): AUC: ↓ 46 % C_{max}: ↓ 38 % Lumefantrine: AUC: ↓ 21 % C_{max}: ↔ Efavirenz: AUC: ↓ 17 % C_{max}: ↔ (CYP3A4 induction)	Since decreased concentrations of artemether, dihydroartemisinin, or lumefantrine may result in a decrease of antimalarial efficacy, caution is recommended when **TRIVAGE TABLETS** and artemether/lumefantrine tablets are co-administered.
Atovaquone and proguanil hydrochloride/Efavirenz (250/100 mg single dose/600 mg daily.)	Atovaquone: AUC: ↓ 75 % (↓ 62 to ↓ 84) C_{max}: ↓ 44 % (↓ 20 to ↓ 61) Proguanil: AUC: ↓ 43 % (↓ 7 to ↓ 65) C_{max}: ↔	Concomitant administration of atovaquone/proguanil with **TRIVAGE TABLETS** should be avoided whenever possible.

[1] This table is not all inclusive

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 the MicrogenicsCedia 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.

Other Interactions:

Efavirenz:

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, cetirizine or paroxetine. Single doses of famotidine or an aluminium and magnesium antacid with simethicone had no effects on efavirenz exposures.

Emtricitabine and tenofovir disoproxil fumarate:

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

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

PREGNANCY AND LACTATION:

Pregnancy:

TRIVAGE TABLETSshould not be used during pregnancy.

Efavirenz: There have been reports of findings consistent with neural tube defects, including meningomyelocele, all in mothers exposed to efavirenz-containing regimens in the first trimester. As neural tube defects occur within the first 4 weeks of foetal development (at which time neural tubes

are sealed), this potential risk would concern women exposed to efavirenz during the first trimester of pregnancy.

Malformations have been observed in foetuses from efavirenz-treated monkeys.

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

Women of childbearing potential should undergo pregnancy testing prior to initiation of treatment with **TRIVAGE TABLETS**.

Breastfeeding: HIV-infected mothers should not breastfeed their infants. Efavirenz, emtricitabine and tenofovir are excreted in human milk. Due to the potential for HIV transmission and the potential for serious adverse reactions in breastfed infants, **mothers should be instructed not to breastfeed if they are taking TRIVAGE TABLETS**.

DOSAGE AND DIRECTIONS FOR USE:

Adults:

The recommended dose of **TRIVAGE TABLETS**is one tablet taken orally once daily.

TRIVAGE TABLETS should be taken on an empty stomach, since food may increase efavirenz exposure and this may cause 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, it is recommended that **TRIVAGE TABLETS** be taken at bedtime.

Children and adolescents:

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

Renal impairment:

TRIVAGE TABLETS is not recommended for patients with moderate to severe impairment of renal function (creatinine clearance < 50 mℓ/min). (see Contraindications).

Where discontinuation of treatment with one of the components of **TRIVAGE TABLETS** is indicated or where dose modification is required, separate preparations of efavirenz, emtricitabine and tenofovir are available. Please refer to the individual package inserts ofthese medicines.

SIDE EFFECTS

EFAVIRENZ

Immune system disorders

Less frequent: Hypersensitivity.

Frequency not known: Immuno-allergic liver injury/failure.

Metabolism and nutrition disorders

Frequent: Weight gain, hypertriglyceridemia.

Less frequent: Hypercholesterolaemia.

Frequency not known: Weight loss, redistribution/accumulation of body fat.

Psychiatric disorders

Frequent: Depression, anxiety, abnormal dreams, insomnia.

Less frequent: Stupor, confusion, impaired concentration, abnormal thinking, agitation, amnesia, delirium, emotional lability, euphoria, hallucination, psychosis, suicide attempt, suicide ideation, completed suicide, paranoia, mania, delusion, neurosis.

Frequency not known: Inappropriate behaviour, apathy.

Nervous system disorders

Frequent: Dizziness, headache, somnolence, cerebellar coordination and balance disturbance, disturbance in attention.

Less frequent: Abnormal coordination, ataxia, convulsions, migraine headaches, neuralgia, paraesthesia, peripheral neuropathy, speech disorder, tremor, hypoaesthesia, amnesia, thinking abnormal, agitation.

Eye disorders

Less frequent: Abnormal vision, blurred vision.

Ear and labyrinth disorders

Less frequent: Tinnitus, vertigo.

Cardiac disorders

Less frequent: Palpitations and tachycardia.

Vascular disorders

Less frequent: Flushing.

Respiratory, thoracic and mediastinal disorders

Less frequent: Asthma, upper respiratory tract infections, sinusitis.

Frequency not known: Dyspnoea.

Gastrointestinal disorders

Frequent: Nausea, vomiting, diarrhoea, abdominal pain.

Less frequent: Gastritis, gastroenteritis, gastro-oesophageal reflux, increased appetite, taste perversion, pancreatitis.

Frequency not known: Constipation, malabsorption.

Hepato-biliary disorders

Frequent: Elevated aspartate aminotransferase (AST), elevated alanine aminotransferase (ALT), elevated gamma-glutamyltransferase (GGT).

Less frequent: Hepatitis, hepatic failure.

Skin and subcutaneous tissue disorders

Frequent: Diffuse maculopapular rash, pruritus.

Less frequent: Severe rash associated with blistering, moist desquamation or ulceration, acne, alopecia, eczema, folliculitis, seborrhoea, skin exfoliation, urticaria, erythema multiforme, photoallergic dermatitis, Stevens-Johnson syndrome.

Frequency not known: Nail disorders, skin discolouration.

Musculoskeletal, connective tissue and bone disorders

Less frequent: Arthralgia, myalgia.

Frequency not known: Myopathy.

Reproductive system and breast disorders

Less frequent: Impotence, decreased libido, increased libido, gynaecomastia.

General disorders and administrative site conditions

Frequent: Fatigue.

Less frequent: Asthenia, malaise, pain, syncope, influenza-like symptoms, alcohol intolerance, hot flushes.

EMTRICITABINE:

Blood and lymphatic system disorders

Frequent: Neutropenia.

Less frequent: Anaemia.

Immune system disorders

Frequent: Allergic reaction.

Metabolism and nutrition disorders

Frequent: Hyperglycaemia, hypertriglyceridaemia.

Frequency not known: Lactic acidosis, usually associated with severe hepatomegaly and steatosis.

Psychiatric disorders

Frequent: Sleep disturbances (abnormal dreams, insomnia).

Frequency not known: Depressive disorder.

Nervous system disorders

Frequent: Headache, dizziness.

Frequency not known: Asthenia, neuropathy, peripheral neuritis, paraesthesia.

Gastrointestinal disorders

Frequent: Nausea, vomiting, diarrhoea, elevated amylase including elevated pancreatic amylase, elevated serum lipase, abdominal pain, dyspepsia.

Hepatobiliary disorders

Frequent: Elevated serum AST and /or elevated serum ALT, hyperbilirubinaemia.

***Skin and subcutaneous tissue dis*orders**

Frequent: Rash event (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash and allergic reaction), skin discolouration, manifested by hyperpigmentation on the palm and/or soles.

Less frequent: Angioedema.

Musculoskeletal and connective tissue disorders

Frequent: Elevated creatine kinase.

Frequency not known: Arthralgia, myalgia.

Respiratory, thoracic and mediastinal disorders

Frequency not known: Increased cough and rhinitis.

General disorders and administration site conditions

Frequent: Pain, asthenia.

TENOFOVIR

Blood and lymphatic system disorders

Frequency not known: Neutropenia, haematuria.

Immune system disorders

Frequency not known: Allergy, allergic reaction.

Metabolism and nutrition disorders

Frequent: Hypophosphataemia.

Less frequent: Hypokalaemia, lactic acidosis, usually associated with severe hepatomegaly and steatosis.

Frequency not known: Hypertriglyceridaemia, hyperglycaemia.

Psychiatric disorders

Frequency not known: Depression, anxiety.

Nervous system disorders

Frequent: Dizziness, headache.

Frequency not known: Peripheral neuropathy (including peripheral neuritis, neuropathy).

Respiratory, thoracic and mediastinal disorders

Frequency not known: Chest pain, pneumonia, dyspnoea.

Gastrointestinal disorders

Frequent: Nausea, vomiting, diarrhoea, abdominal pain, abdominal distension, flatulence, dyspepsia and anorexia.

Less frequent: Raised serum amylase concentration, pancreatitis.

Hepatobiliary disorders

Frequent: Increased transaminases.

Less frequent: Hepatic steatosis, hepatitis.

***Skin and subcutaneous tissue disorders*:**

Frequent: Skin rashes (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash).

Less frequent: Angioedema.

Musculoskeletal and connective tissue disorders

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

Frequency not known: Back pain, arthralgia, myalgia.

***Renal and urinary disorders*:**

Less frequent: Proteinuria, proximal renal tubulopathy including Fanconi syndrome, renal failure (acute and chronic), acute tubular necrosis, nephritis (including acute interstitial nephritis), nephrogenic diabetes insipidus.

Frequency not known: Renal impairment.

***General disorders and administration site conditions*:**

Frequent: Asthenia.

Frequency not known: Fever, sweating, weight loss.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

In the event of overdose, the patient must be monitored for evidence of toxicity, and standard supportive treatment given as necessary.

Efavirenz:

Symptoms of overdose include increased nervous system symptoms and involuntary muscle contractions. Treatment of efavirenz overdose should consist of general supportive measures. These should include vital sign monitoring and observation of the patient's clinical status. Activated charcoal may be administered to aid removal of unabsorbed medicine. Dialysis is unlikely to significantly remove efavirenz from the blood, since the medicine is highly protein bound.

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 four-hour haemodialysis session removes approximately 10 % of the administered tenofovir dose.

IDENTIFICATION:

Pink, capsule shaped, biconvex, film-coated tablets debossed with “CL 81” on one side and plain on the other side.

PRESENTATION:

HDPE Container Pack:

For 28 or 30 tablets:

Tablets are packed in a white, opaque, round 100 ml (28 tablets) or 120 ml HDPE container with 38 mm neck finish containing two silica gel sachets and closed with a 38 mm white opaque polypropylene stock ribbed closure with wad having induction sealing liner, packed in a carton. Each container contains 28 or 30 tablets.

For 84 or 90 tablets:

Tablets are packed in a white, opaque, round 250 ml (84 tablets or 90 tablets) HDPE container with 53 mm neck finish containing two silica gel sachets and closed with a 53 mm child resistant or continuous thread closure with pulp heat seal liner, packed in a carton. Each container contains 84 or 90 tablets.

STORAGE INSTRUCTIONS:

Store at or below 25 °C. Protect from light and moisture.

Keep the HDPE containers closed.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

51/20.2.8/0120

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Macleods Pharmaceuticals SA (Pty) Ltd

Office Block 1, Bassonia Estate Office Park (East)

1 Cussonia Drive, Bassonia Rock, Ext 12

Alberton, 2190

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

29 September 2017

PM0059-01

Vanita Rajool

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