SCHEDULING STATUS:
S4

PROPRIETARY NAME (AND DOSAGE FORM):
TRIOLAR 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).

WARNING
LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES, ALONE OR IN COMBINATION WITH OTHER ANTIRETROVIRALS (SEE **WARNINGS AND SPECIAL PRECAUTIONS**).
SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO HAVE DISCONTINUED EMTRICITABINE OR TENOFOVIR, WHICH ARE COMPONENTS OF **TRIOLAR TABLETS**. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE **TRIOLAR TABLETS** AND ARE COINFECTED WITH HIV AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE **WARNINGS AND SPECIAL PRECAUTIONS**).

PHARMACOLOGICAL CLASSIFICATION:
A 20.2.8 Antimicrobial (chemotherapeutic) agents. Antiviral agents.

PHARMACOLOGICAL ACTION:
Pharmacodynamic properties:
TRIOLAR TABLETS is a fixed dose combination tablet containing efavirenz, emtricitabine and tenofovir disoproxil fumarate (tenofovir DF). Efavirenz is a non-nucleoside reverse transcriptase inhibitor; 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 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'-triphosphate and 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 disoproxil fumarate:
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 EC_{90} 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 agents may therefore develop in patients whose virus harbours either or both of these amino acid substitutions.

TRIOLAR TABLETS
PM03311101

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 radiolabelled 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 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[1]

	Emtricitabine	Tenofovir
Fasted Oral Bioavailability[2] (%)	92 (83,1 – 106,4)	25 (NC – 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:
TRIOLAR 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. **TRIOLAR 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 **CONTRA-INDICATIONS, 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 SPECIAL PRECAUTIONS**).
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:
TRIOLAR TABLETS is indicated as mono- or combination therapy for HIV-1 infection in adults.

CONTRA-INDICATIONS:
TRIOLAR TABLETS is contra-indicated in patients:
- With previously demonstrated hypersensitivity to emtricitabine, tenofovir or efavirenz or any of the other components of the product.
- 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 astemizole, cisapride, midazolam, triazolam or ergot derivatives, because competition for CYP3A4 by the efavirenz in **TRIOLAR 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. Since **TRIOLAR TABLETS** is a fixed-dose combination product, the dose of efavirenz cannot be altered; therefore voriconazole and **TRIOLAR TABLETS** must not be co-administered.
- Who are pregnant or breastfeeding (see **PREGNANCY AND LACTATION**).

WARNINGS AND SPECIAL PRECAUTIONS:
Lactic acidosis / hyperlactataemia:
Use of **TRIOLAR 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 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 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 **TRIOLAR TABLETS** to patients with known factors for liver disease.

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

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

Patients with HIV and hepatitis B or C virus co-infection:
Patients with chronic hepatitis B or C and treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions.
Medical practitioners should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV).
In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant package inserts for these medicines.
Patients co-infected with HIV and HBV who discontinue **TRIOLAR TABLETS** 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 **TRIOLAR TABLETS** therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis.

Coadministration with related medicines
Related medicines not for co-administration with **TRIOLAR TABLETS** include emtricitabine, tenofovir DF, emtricitabine/tenofovir DF and efavirenz which contain the same active components as **TRIOLAR TABLETS**. Due to similarities between emtricitabine and lamivudine, **TRIOLAR TABLETS** should not be co-administered with medicines containing lamivudine, including lamivudine/zidovudine, lamivudine, and abacavir.

Renal impairment:
Emtricitabine and tenofovir, two of the active ingredients in **TRIOLAR TABLETS**, are principally eliminated by the kidney. **TRIOLAR TABLETS** should not be administered to patients with creatinine clearance < 50 mℓ/min.
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 **TRIOLAR TABLETS**. Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment.
The use of **TRIOLAR TABLETS** should be avoided in patients who are concurrently taking or who have recently taken a nephrotoxic agent.

Medicine Interactions (**see INTERACTIONS*****)***
Concomitant use of **TRIOLAR TABLETS** 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.

Psychiatric Symptoms
Serious psychiatric adverse events have been reported in patients treated with efavirenz. In controlled trials of patients treated with regimens containing efavirenz, the frequency of specific serious psychiatric events among patients who received efavirenz or control regimens, respectively, were: severe depression (2,4 %, 0,9 %), suicidal ideation (0,7 %, 0,3 %), nonfatal suicide attempts (0,5 %, 0 %), aggressive behavior (0,4 %, 0,5 %), paranoid reactions (0,4 %, 0,3 %), and manic reactions (0,2 %, 0,3 %). When psychiatric symptoms similar to those noted above were combined and evaluated as a group in a multifactorial analysis of data, treatment with efavirenz was associated with an increase in the occurrence of these selected psychiatric symptoms. Other factors associated with an increase in the occurrence of these psychiatric symptoms were history of injection drug use, psychiatric history, and receipt of psychiatric medication at study entry; similar associations were observed in both the efavirenz and control treatment groups.
One percent of efavirenz-treated subjects discontinued or interrupted treatment because of one or more of these selected psychiatric symptoms. There have also been post-marketing reports of death by suicide, delusions, and psychosis-like behaviour; although 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, and if so, to determine whether the risks of continued therapy outweigh the benefits (see **SIDE EFFECTS**).

Nervous System Symptoms
53 % of patients receiving efavirenz in controlled trials reported central nervous system symptoms compared to 25 % of patients receiving control regimens. These symptoms included dizziness (28,1 %), insomnia (16,3 %), impaired concentration (8,3 %), somnolence (7,0 %), abnormal dreams (6,2 %) and hallucinations (1,2 %). Other reported symptoms were euphoria, confusion, agitation, amnesia, stupor, abnormal thinking, and depersonalization. The majority of these symptoms were mild to moderate (50,7 %); symptoms were severe in 2,0 % of subjects. Overall, 2,1 % of subjects discontinued therapy as a result. These symptoms usually begin during the first or second day of therapy and generally resolve after the first 2–4 weeks of therapy. After 4 weeks of therapy, the prevalence of nervous system symptoms of at least moderate severity ranged from 5 % to 9 % in subjects treated with regimens containing efavirenz and from 3 % to 5 % in subjects treated with a control regimen. Patients should be informed that these common symptoms were likely to improve with continued therapy and were not predictive of subsequent onset of the less frequent psychiatric symptoms. Dosing at bedtime may improve the tolerability of these nervous system symptoms.
Patients receiving **TRIOLAR TABLETS** should be alerted to the potential for additive central nervous system effects when **TRIOLAR TABLETS** is used concomitantly with alcohol or psychoactive medicines.
Patients who experience central nervous system symptoms such as dizziness, impaired concentration, and/or drowsiness should avoid potentially hazardous tasks such as driving or operating machinery.

There have been reports of nervous system symptoms with efavirenz use (see **SIDE EFFECTS**). In addition, psychosis-like reactions, including delusions and inappropriate behaviour (including aggressive reactions), have also been reported. These reactions occurred predominantly in patients with a history of mental illness or substance abuse. There have been infrequent reports of severe acute depression (including suicidal ideation/attempts) in both efavirenz-treated and control-treated patients, predominantly in patients with a previous history of depression. Patients should be advised to contact their doctor immediately if they experience these symptoms since discontinuation of **TRIOLAR TABLETS** may be required.

Skin rash:
Mild-to-moderate rash, which usually resolves 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 **TRIOLAR TABLETS** should be discontinued in patients who experience severe rash associated with blistering, desquamation, mucosal involvement or fever.

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.

Cholesterol:
Monitoring of cholesterol and triglyceride levels should be considered in patients treated with **TRIOLAR TABLETS** (see **SIDE EFFECTS**).

Bone effects:
TRIOLAR 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.

Lipodystrophy and metabolic abnormalities
Combination antiretroviral therapy has been associated with the redistribution/accumulation of body fat, including central obesity, dorso-cervical fat, enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and elevated serum lipid and glucose levels in HIV patients. Clinical examination should include evaluation for physical signs of fat redistribution. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

Immune Reconstitution Inflammatory Syndrome
Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination Anti-Retroviral Therapy (cART). Typically 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.

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

Opportunistic infections
Patients receiving **TRIOLAR 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 **TRIOLAR 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 use:
The safety and efficacy of **TRIOLAR TABLETS** in children have not been established.

Use in the elderly:
Clinical studies of fixed dose combinations of emtricitabine and tenofovir, as in **TRIOLAR 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 medicinal therapy.

Effects on the ability to drive and use machines:
TRIOLAR TABLETS may 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 *in vivo* to induce CYP3A4. Other compounds that are substrates of CYP3A4 may have decreased plasma concentrations when coadministered with efavirenz. *In vitro* studies have demonstrated that efavirenz inhibits 2C9, 2C19, and 3A4 isozymes in the range of observed efavirenz plasma concentrations. Coadministration of efavirenz with medicines primarily metabolised by these isozymes may result in altered plasma concentrations of the coadministered medicine. Therefore, appropriate dose adjustments may be necessary for these medicines.
Medicines that induce CYP3A4 activity (e.g., phenobarbital, rifampin, 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 **TRIOLAR 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 acyclovir, adefovir dipivoxil, cidofovir, ganciclovir, valacyclovir, and valganciclovir.
Co-administration of tenofovir DF 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 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. **TRIOLAR 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 **TRIOLAR 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 agents or are potential medicine interactions; no medicine interaction studies have been conducted using **TRIOLAR TABLETS**. The tables include potentially significant interactions, but are not all inclusive.

Table: 2 Medicines that are contra-indicated or not recommended for use with TRIOLAR TABLETS

Medicine Class: Medicine Name	Clinical Comment
Antifungal: voriconazole	CONTRA-INDICATED 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)	CONTRA-INDICATED 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 **TRIOLAR TABLETS** because the active ingredients- emtricitabine, tenofovir DF, emtricitabine/tenofovir DF and efavirenz are components of **TRIOLAR TABLETS**. Lamivudine is similar to emtricitabine.
Benzodiazepines: midazolam, triazolam	CONTRA-INDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.
Calcium channel blocker: bepridil	CONTRA-INDICATED due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.
GI motility medicine: cisapride	CONTRA-INDICATED due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.
Neuroleptic: pimozide	CONTRA-INDICATED due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.
St. John's wort *(Hypericum perforatum)*	NOT RECOMMENDED: 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 on Medicine Interaction Trials 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 **TRIOLAR 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 **TRIOLAR TABLETS** is administered with fosamprenavir once daily. No change in the ritonavir dose is required when **TRIOLAR TABLETS** is administered with fosamprenavir/ritonavir once daily. No change in the ritonavir dose is required when **TRIOLAR 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 **TRIOLAR TABLETS**. Therefore co-administration of **TRIOLAR 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. TRIOLAR 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 **TRIOLAR TABLETS** is used in combination with ritonavir.
Protease Inhibitor: Saquinavir	↑ saquinavir concentration	Should not be used as sole protease inhibitor in combination with **TRIOLAR 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 TRIOLAR TABLETS. Data are not available to recommend a dose adjustment of didanosine for patients weighing less than 60 kg.** When co-administered, **TRIOLAR 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 **TRIOLAR TABLETS** should be under fasted conditions. **Co-administration of TRIOLAR TABLETS and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse events.**
Other agents		
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 **TRIOLAR TABLETS**. Alternative anticonvulsant treatment should be used.
Phenytoin Phenobarbital	↓ anticonvulsant concentration ↓ efavirenz concentration	Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.
Antidepressant : Sertraline.	↓ sertraline concentration	Increases in sertraline dose should be guided by clinical response.
Antifungals: Itraconazole	↓ itraconazole concentration ↓ hydroxy-itraconazole concentration	Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered.
Ketoconazole	↓ ketoconazole concentration	Medicine interaction studies with **TRIOLAR 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 **TRIOLAR 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 **TRIOLAR 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 **TRIOLAR 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 **TRIOLAR 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.

[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 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.

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, 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 agents and tenofovir DF.

PREGNANCY AND LACTATION:
The use of **TRIOLAR TABLETS** during pregnancy is contra-indicated as teratogenicity with efavirenz in pregnancy has been demonstrated (see **CONTRA-INDICATIONS**).
Barrier contraception should always be employed in combination with other contraceptive methods (e.g., oral or other hormonal contraceptives).
Women of childbearing potential should undergo pregnancy testing prior to initiation of treatment with **TRIOLAR TABLETS** (see **CONTRA-INDICATIONS**).
Breastfeeding mothers: HIV-infected mothers should not breastfeed their infants. 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 TRIOLAR TABLETS**.

DOSAGE AND DIRECTIONS FOR USE:
Adults:
The recommended dose of **TRIOLAR TABLETS** is one tablet taken orally once daily.
TRIOLAR 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 **TRIOLAR TABLETS** be taken at bedtime.
Children and adolescents:
TRIOLAR TABLETS is not recommended for use in children below 18 years of age due to lack of data on safety and efficacy (see **CONTRA-INDICATIONS**).
Renal impairment:
TRIOLAR TABLETS is not recommended for patients with moderate to severe impairment of renal function (creatinine clearance < 50 mℓ/min).

Where discontinuation of treatment with one of the components of **TRIOLAR 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 of these medicines.

SIDE EFFECTS:
EFAVIRENZ (600 mg):
Metabolism and nutrition disorders:
Frequency not known: Weight gain and weight loss, redistribution/accumulation of body fat, hypercholesterolaemia, hypertriglyceridaemia.
Psychiatric disorders:
Less frequent: Stupor, confusion, impaired concentration, insomnia, anxiety, abnormal dreams, depression, abnormal thinking, agitation, amnesia, delirium, emotional lability, euphoria, hallucination, psychosis.
Frequency not known: Delusions, inappropriate behaviour, severe acute depression (including suicide ideation and attempt), neurosis, paranoia, apathy, mania.
Nervous system disorders:
Frequent: Dizziness, headache, somnolence.
Less frequent: Abnormal coordination, ataxia, convulsions, migraine headaches, neuralgia, paraesthesia, peripheral neuropathy, speech disorder, tremor, hypoesthesia.
Eye disorders:
Less frequent: Abnormal vision.
Ear and labyrinth disorders:
Less frequent: Tinnitus, vertigo.
Cardiac disorders:
Less frequent: Flushing, palpitations and tachycardia.
Respiratory, thoracic and mediastinal disorders:
Less frequent: Asthma, upper respiratory tract infections, sinusitis.
Frequency not known: Dyspnoea.
Gastrointestinal disorders:
Frequent: Nausea, vomiting, diarrhoea.
Less frequent: Gastritis, gastroenteritis, gastro-oesophageal reflux, increased appetite, taste perversion.
Frequency not known: Constipation, malabsorption.
Hepato-biliary disorders:
Less frequent: Hepatitis.
Frequency not known: Increased hepatic enzymes, hepatic failure.
Skin and subcutaneous tissue disorders:
Frequent: Diffuse maculopapular rash.
Less frequent: Severe rash associated with blistering, moist desquamation or ulceration, acne, alopecia, eczema, folliculitis, seborrhoea, skin exfoliation, urticaria.
Frequency not known: Flushing, erythema multiforme, nail disorders, photoallergic dermatitis, skin discolouration, Stevens-Johnson syndrome.
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.
Frequency not known: Gynaecomastia.
Immune system disorders:
Frequency not known: Allergic reaction.
General disorders and administrative site conditions:
Frequent: Fatigue.
Less frequent: Asthenia, malaise, pain, syncope, influenza-like symptoms, alcohol intolerance, hot flushes.

EMTRICITABINE (200 mg):
Nervous system disorders:
Frequent: Headache.
Frequency not known: Asthenia, dizziness, neuropathy, peripheral neuritis, paraesthesia.
Psychiatric disorders:
Frequency not known: Sleep disturbances (abnormal dreams, insomnia), depressive disorder.
Gastrointestinal disorders:
Frequent: Nausea, vomiting, diarrhoea
Frequency not known: Abdominal pain, dyspepsia.
Skin and subcutaneous tissue disorders:
Frequent: Rash event (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash and allergic reaction).
Frequency not known: Skin discolouration, manifested by hyperpigmentation on the palm and/or soles.
Musculoskeletal and connective tissue disorders:
Frequency not known: Arthralgia, myalgia.
Blood and lymphatic system disorders:
Frequency not known: Neutropenia, anaemia.
Renal and urinary disorders:
Frequent: Elevation of creatinine kinase.
Respiratory, thoracic and mediastinal disorders:
Frequency not known: Increased cough and rhinitis.
Hepatobiliary disorders:
Frequency not known: Raised liver enzyme concentrations and hyperbilirubinaemia.
Metabolism and nutrition disorders:
Frequency not known: Lactic acidosis, usually associated with severe hepatomegaly and steatosis, hypertriglyceridaemia, hyperglycaemia.

TENOFOVIR (300 mg):
Gastrointestinal disorders:
Frequent: Nausea, vomiting, diarrhoea, abdominal pain, flatulence, dyspepsia and anorexia.
Less frequent: Raised serum amylase concentration, pancreatitis.
Frequency not known: Abdominal pain, dyspepsia.
Nervous system disorders:
Frequency not known: Headache, asthenia, dizziness, peripheral neuropathy (including peripheral neuritis, neuropathy).
Psychiatric disorders:
Frequency not known: Depression, anxiety.
Skin and subcutaneous tissue disorders:
Frequency not known: Skin rashes (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash).
Musculoskeletal and connective tissue disorders:
Frequency not known: Back pain, arthralgia, myalgia.
Respiratory, thoracic and mediastinal disorders:
Frequency not known: Chest pain, pneumonia, dyspnoea.
Blood and lymphatic system disorders:
Frequency not known: Neutropenia, haematuria.
Hepatobiliary disorders:
Frequency not known: Raised liver enzymes and hepatitis.
Metabolism and nutrition disorders:
Frequent: Hypophosphataemia.
Frequency not known: Lactic acidosis, usually associated with severe hepatomegaly and steatosis, hypertriglyceridaemia, hyperglycaemia.
Renal and urinary disorders:
Frequency not known: Increased creatinine kinase levels, nephritis, nephrogenic diabetes insipidus, renal impairment, acute renal failure, and effects on the renal proximal tubules including Fanconi syndrome, renal failure, proximal tubulopathy, proteinuria, acute tubular necrosis.
Immune system disorders:
Frequency not known: Allergy, allergic reaction.
General disorders:
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:
Increased nervous system symptoms and involuntary muscle contractions have been reported in patients taking 600 mg twice daily. 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 emtricitabine 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:
Tablets are packed in white, opaque, round 100 mℓ (28 tablets) or 120 mℓ (30 tablets) HDPE container with 38 mm neck finish closed with 38 mm white opaque polypropylene stock ribbed closure with wad having induction sealing liner. Each container contains 28 or 30 tablets.

STORAGE INSTRUCTIONS:
Store at or below 25 °C. Protect against light.
Keep the HDPE container tightly closed.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:
47/20.2.8/1006.

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.

DATE OF PUBLICATION OF THIS PACKAGE INSERT:
The date on the registration certificate: 5 June 2014
The date of the most recently revised package insert as approved by Council: 17 February 2017

PATIENT INFORMATION LEAFLET

SCHEDULING STATUS: S4

PROPRIETARY NAME, STRENGTH AND PHARMACEUTICAL FORM
TRIOLAR TABLETS (Film-coated tablets)
Efavirenz 600 mg, emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg

Read all of this leaflet carefully before you start taking **TRIOLAR TABLETS.**
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- **TRIOLAR TABLETS** has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

WHAT TRIOLAR TABLETS CONTAIN
Each film coated tablet contains 600 mg efavirenz, 200 mg emtricitabine and 300 mg of tenofovir disoproxil fumarate.

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). Sugar free.

WHAT TRIOLAR TABLETS ARE USED FOR
TRIOLAR TABLETS is used to treat Human Immunodeficiency Virus (HIV) infection in adults. **TRIOLAR TABLETS** is used alone or in combination with other anti-HIV medicines to treat patients with HIV-1 infection.

BEFORE YOU TAKE TRIOLAR TABLETS
Do not take TRIOLAR TABLETS:
- if you are hypersensitive (allergic) to efavirenz, emtricitabine and tenofovir disoproxil fumarate, or any of the other ingredients of **TRIOLAR TABLETS**.
- if you have kidney problems.
- if you are pregnant or breastfeeding.
- if you are currently taking any of the following medicines:
  - astemizole (used to treat hay fever or other allergies)
  - cisapride (used to treat heartburn)
  - bepridil (used to treat heart disease)
  - ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine) (used to treat migraines and cluster headaches)
  - midazolam or triazolam (used to help you sleep)
  - pimozide (used to treat certain mental conditions)
  - voriconazole (for fungal infections).

If you are taking any of these medicines, tell your doctor immediately. Taking these medicines with **TRIOLAR TABLETS** could cause serious or life-threatening side effects or stop these medicines from working properly.

Take special care with TRIOLAR TABLETS:

TRIOLAR TABLETS may lead to serious problems with your liver or cause too much acid in your blood. If left untreated, this may cause death. You should be closely monitored by your doctor for several months if you are infected with HBV and discontinue the use of TRIOLAR TABLETS.

- **TRIOLAR TABLETS** may cause lactic acidosis, together with an enlarged liver, which can be fatal. Deep, rapid breathing, drowsiness, and symptoms such as nausea, vomiting and stomach pain, might indicate the development of lactic acidosis. Lactic acidosis occurs more often in women. Patients who are overweight are more at risk.
- Tell your doctor if you have liver disease (including hepatitis B). Independent of a history of liver disease, your doctor will consider regular blood tests to check how your liver is working.
- Take your child, if exposed during pregnancy to **TRIOLAR TABLETS**, to your doctor immediately if your child appears pale, weak, sleepy all the time, is breathing faster, the heart is beating faster, the child does not appear to be putting on weight, is vomiting, has fever, sore throat, mouth ulcers, appears stiff, has convulsions (fits) or behaving abnormally. Your doctor will perform additional medical and laboratory tests on your child.
- **TRIOLAR TABLETS** may cause inflammation of the pancreas. Inform your doctor if you experience severe upper stomach pain with nausea (feeling sick) and vomiting.
- Inform your doctor if you have had any liver disease including hepatitis B or C, as treatment with **TRIOLAR TABLETS** in patients with liver disease could cause severe side-effects affecting the liver including death. Your doctor will monitor your liver function by performing blood tests on a regular basis.
- If you have an ongoing hepatitis B infection, do not stop **TRIOLAR TABLETS** without your doctor's advice, as your hepatitis may come back. The hepatitis may be more severe if you also have a serious liver disease.
- Tell your doctor if you are taking other medicines that contain efavirenz, emtricitabine, tenofovir disoproxil, or lamivudine or adefovir dipivoxil. **TRIOLAR TABLETS** should not be taken with any of these medicines.
- Tell your doctor if you are taking St. John's wort (*Hypericum perforatum*) (a herbal remedy used for depression and anxiety). St. John's wort and **TRIOLAR TABLETS** should not be taken simultaneously.
- Tell your doctor if you have had kidney disease, or if tests have shown problems with your kidneys. **TRIOLAR TABLETS** may affect your kidneys.
- **TRIOLAR TABLETS** is not usually taken with other medicines that can damage your kidneys. If this is unavoidable, your doctor will monitor your kidney function.
- Rashes may be caused by **TRIOLAR TABLETS**. If you see any signs of a severe rash with blistering or fever, stop taking **TRIOLAR TABLETS** and tell your doctor at once.
- Tell your doctor if you have a history of mental illness, including depression, or of substance or alcohol abuse. Tell your doctor immediately if you feel depressed, have suicidal thoughts or have strange thoughts.
- Tell your doctor if you ever had seizures or are taking medicines for seizures.
- Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms inform your doctor.
- **TRIOLAR TABLETS** decreases bone mineral density which could result in fractures. Your doctor may prescribe calcium and vitamin D supplements while taking **TRIOLAR TABLETS.**
- **TRIOLAR TABLETS** may change your body shape, by changing the way body fat is distributed. You may lose fat from your legs, arms and face and/or gain fat around the abdomen (tummy) and internal organs; get larger breasts or fatty lumps on the back of the neck (buffalo hump).
- If you have advanced HIV infection (AIDS) and have any infection, you may develop acute symptoms of the infection or inflammation and a worsening of the symptoms of an existing infection once treatment with **TRIOLAR TABLETS** is started. If you notice signs of inflammation or infection, or deterioration thereof, tell your doctor at once.
- You will need to take **TRIOLAR TABLETS** every day. **TRIOLAR TABLETS** helps to control your condition and delay disease progression, but it is not a cure for HIV infection. You may continue to develop other infections and other illnesses associated with HIV disease. You should keep in regular contact with your doctor. Do not stop taking your medicine without first talking to your doctor.
- Treatment with **TRIOLAR TABLETS** does not reduce the risk of passing HIV infection on to others by unprotected sexual contact or by blood transfer (for example, blood transfusions or sharing needles). You should continue to use appropriate precautions to prevent this.
- The safety and effectiveness of **TRIOLAR TABLETS** in children and patients younger than 18 years has not been determined.
- **TRIOLAR TABLETS** is not recommended for the elderly who are more than 65 years of age.
- **TRIOLAR TABLETS** may increase blood cholesterol, triglyceride and sugar levels and your doctor will perform blood tests at regular intervals to monitor cholesterol, triglyceride and sugar levels.

Taking TRIOLAR TABLETS with food and drink:
TRIOLAR TABLETS should be taken without food. Alcohol should be avoided.

PREGNANCY AND BREASTFEEDING :
Pregnancy:
- You should not become pregnant if you are taking **TRIOLAR TABLETS**. Malformations have been seen in foetuses from animals treated with **TRIOLAR TABLETS** during pregnancy.
- Inform your doctor immediately if you are pregnant or intend to become pregnant.
- If you are a woman receiving **TRIOLAR TABLETS**, a reliable form of barrier contraception (for example, a condom), should always be used with other methods of contraception including oral (pill) or other hormonal contraceptives (for example, implants, injection).
- Do not take **TRIOLAR TABLETS** if you are pregnant.

Breastfeeding:
- Do not breastfeed if you are taking **TRIOLAR TABLETS** as it may cause serious harm to your baby. If you have HIV you should not breastfeed under any circumstances as you may pass the HIV to your baby.

If you are pregnant or breastfeeding your baby, please consult your doctor, pharmacist or other healthcare professional for advice before taking **TRIOLAR TABLETS.**

Driving and Using Machinery
TRIOLAR TABLETS can cause dizziness, impaired concentration and/or drowsiness. If you feel dizzy or drowsy while taking **TRIOLAR TABLETS** do not drive and do not use any tools or machines.

Taking other medicines with TRIOLAR TABLETS:

Always tell your healthcare professional if you are taking any other medicine. (This includes complementary or traditional medicines)

- Tell your doctor if you are taking, or have recently taken any other medicines.
- Tell your doctor if you are taking efavirenz, abacavir, emtricitabine, tenofovir, indinavir or lamivudine (for HIV infection).
- If you are currently taking any of the following medicines:
  - cisapride (used to treat heartburn)
  - bepridil (used to treat heart disease)
  - ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine) (used to treat migraines and cluster headaches)
  - midazolam or triazolam (used to help you sleep)
  - pimozide (used to treat certain mental conditions)
  - voriconazole (for fungal infections).

If you are taking any of these medicines, tell your doctor immediately.

- Tell your doctor if you are taking atazanavir and/or lopinavir/ritonavir (for HIV infection): If you are taking any of these medicines, your doctor may need to monitor your therapy more closely or you may not be able to use **TRIOLAR TABLETS**.
- Tell your doctor if you are taking other medicines containing didanosine (for HIV infection). Taking **TRIOLAR TABLETS** with other antiviral medicines that contain didanosine can raise the levels of didanosine in your blood. Inflammation of the pancreas and neuropathy (disorders with the nerves) can occur. Your doctor will carefully consider whether to treat you with combinations of tenofovir and didanosine.
- Medicines used to lower blood fats (also called statins): Atorvastatin, pravastatin, simvastatin. **TRIOLAR TABLETS** can reduce the amount of statins in your blood. Your doctor will check your cholesterol levels and will consider changing the dose of your statin, if needed.
- Medicines used to treat convulsions/seizures (anticonvulsants): Carbamazepine, phenytoin, phenobarbital. **TRIOLAR TABLETS** can reduce the amount of the anticonvulsant in your blood. Carbamazepine can reduce the amount of efavirenz, one of the components of **TRIOLAR TABLETS**, in your blood. Your doctor may need to consider giving you a different anticonvulsant.
- Medicines used to treat bacterial infections: Clarithromycin, rifabutin, rifampicin. Your doctor may need to consider changing your dose or giving you an alternative antibiotic. In addition, your doctor may consider giving you an additional dose of efavirenz to treat your HIV infection.
- Medicines used to treat fungal infections (antifungals): Itraconazole or ketoconazole. **TRIOLAR TABLETS** can reduce the amount of itraconazole or ketoconazole in your blood. Your doctor may need to consider giving you a different antifungal.
- Hormonal contraceptive, such as birth control pills, an injected contraceptive (for example, Depo-Provera), or a contraceptive implant: You must also use a reliable barrier method of contraception such as a condom as **TRIOLAR TABLETS** may make hormonal contraceptives less likely to work.
- Methadone, a medicine used to treat addiction, as your doctor may need to change your methadone dose.
- Sertraline, a medicine used to treat depression, as your doctor may need to change your dose of sertraline.
- Diltiazem or similar medicines (called calcium channel blockers): When you start taking **TRIOLAR TABLETS**, your doctor may need to adjust your dose of the calcium channel blocker.
- Warfarin (a medicine used to reduce clotting of the blood): Your doctor may need to adjust your dose of warfarin.
- St. John's wort (*Hypericum perforatum*) (a herbal remedy used for depression and anxiety) is not recommended to take with **TRIOLAR TABLETS.**
- Tell your doctor if you are taking other medicines that may reduce your kidney function. Some examples include
  - Aminoglycosides (for bacterial infection)
  - Adefovir dipivoxil (for viral infection)
  - Cidofovir (for viral infection)
  - Acyclovir(for viral infection)
  - Valacyclovir(for viral infection)
  - Ganciclovir(for viral infection)
  - Valganciclovir(for viral infection)
  - Amphotericin B (for fungal infection)
  - Foscarnet (for viral infection)
  - Pentamidine (for infections)
  - Interleukin-2 (to treat cancer)

HOW TO TAKE TRIOLAR TABLETS

Always take TRIOLAR TABLETS exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure. If you have the impression that the effect of TRIOLAR TABLETS is too strong or too weak for you, tell your doctor or pharmacist.

- Stay under a healthcare provider's care when taking **TRIOLAR TABLETS.** Do not change your treatment or stop treatment without first talking with your healthcare provider.
- The usual dose of **TRIOLAR TABLETS** is one tablet, swallowed with water, once a day at bedtime, taken without food.

If you take more TRIOLAR TABLETS than you should:
- Seek emergency medical attention if you think you have taken too much of **TRIOLAR TABLETS.**

In the event of overdosage consult your doctor or pharmacist. If neither is available contact the nearest hospital or poison control center.

If you forget to take TRIOLAR TABLETS:
If you forget to take a dose, take it as soon as you remember, and then continue as before. Do not take a double dose to make up for forgotten individual dose.

POSSIBLE SIDE EFFECTS
TRIOLAR TABLETS can have side effects.
Not all the side effects reported for **TRIOLAR TABLETS** are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking **TRIOLAR TABLETS,** please consult your doctor, pharmacist or healthcare professional for advice.

Get emergency medical help if you have any of these **signs of an allergic reaction:**
- Hives; difficulty breathing; swelling of your face, lips, tongue, or throat.

Call your doctor at once if you have any of the following side effects:
- Lactic acidosis (severe increase of lactic acid in the blood, a serious side effect that can be fatal) – The following side effects may be signs of lactic acidosis: deep rapid breathing, drowsiness, feeling sick (nausea), being sick (vomiting) and stomach pain.
- Liver damage – nausea; stomach pain; low fever; loss of appetite; dark urine; clay-coloured stools; jaundice (yellowing of the skin or eyes).
- Back pain caused by kidney problems, including kidney failure. Your doctor may do blood tests to see if your kidneys are working properly.
- Fever, chills, sore throat, cough, or other signs of infection.
- Psychiatric symptoms including confusion, severe depression, suicidal thoughts, aggression, extreme fear, hallucinations, or unusual behaviour.
- Fever with a severe blistering, peeling and red skin rash or any severe skin reaction.
- Seizures (have a "fit" or convulsion).

Tell your doctor if you notice any of the following side effects or if any of these symptoms are bothersome or do not go away:
Frequent side effects:
- fatigue
- dizziness, drowsiness
- headache
- nausea, vomiting, diarrhoea, stomach pain, indigestion, upset stomach

Less frequent side effects:
- numbness, tingling, pins and needles, tremors (shake)
- difficulty concentrating, forgetfulness, confusion
- difficulty falling asleep, unusual dreams
- disturbances of co-ordination and balance
- abnormally happy mood
- feeling depressed or anxious
- blurred vision
- ringing in the ears, a feeling of spinning or tilting (vertigo)
- sinusitis
- palpitations (rapid irregular action of heart), increased rate of heart beat
- asthma
- increased appetite, lack of appetite
- taste disturbances
- inflammation of the pancreas (severe pain in the abdomen)
- skin rash, itching, increased sweating, eczema, loss of hair, acne, changes in skin and nail colour
- muscle or joint pain
- impotence (loss of male sexual ability); increased and decreased sexual drive (libido)
- lack of energy, generally feeling unwell
- hot flushes

Frequency not known:
- flu-like symptoms, cough, runny or stuffy nose
- pain, back pain, chest pain
- shortness of breath
- constipation
- enlarged breasts in males
- blood in the urine, inflammation of the kidney, passing a lot of urine and feeling thirsty
- weight gain or weight loss, changes in shape or location of body fat (especially in your arms, legs, face, neck, breasts, and waist)

Blood tests may also show:
- decreases in phosphate levels in the blood
- increased levels of creatine kinase in the blood that may result in muscle pain and weakness
- anaemia (low red blood cell count)
- low white blood cell count (a reduced white blood cell count can make you more prone to infection)
- increased fatty acids (triglycerides), bilirubin or sugar levels in the blood
- liver and pancreas problems
- decreases in potassium in the blood
- increases in creatinine in the blood
- proteins in urine

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

STORING AND DISPOSING OF TRIOLAR TABLETS
Store at or below 25 °C (room temperature). Protect against light.
Keep the HDPE container tightly closed.
KEEP ALL MEDICINES OUT OF REACH OF CHILDREN.

Return all unused medicine to your pharmacist.
Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

PRESENTATION:
TRIOLAR TABLETS:
HDPE Container Pack:
Tablets are packed in white, opaque, round 100 mℓ (28 tablets) or 120 mℓ (30 tablets) HDPE container with 38 mm neck finish closed with 38 mm white opaque polypropylene stock ribbed closure with wad having induction sealing liner. Each container contains 28 or 30 tablets.

IDENTIFICATION
TRIOLAR TABLETS
Pink, capsule shaped, biconvex, film-coated tablets debossed with "CL 81" on one side and plain on the other side.

REGISTRATION NUMBER/REFERENCE NUMBER
47/20.2.8/1006.

NAME AND ADDRESS OF REGISTRATION HOLDER
Macleods Pharmaceuticals SA (Pty) Ltd
Office Block 1
Bassonia Estate Office Park (East)
1 Cussonia Drive
Bassonia Rock, Ext. 12
Alberton.

DATE OF PUBLICATION
The date on the registration certificate: 5 June 2014
The date of the most recently revised patient information leaflet as approved by Council: 17 February 2017

SKEDULERINGSTATUS:
S4

EIENDOMSNAAM (en doseervorm):
TRIOLAR TABLETS (Filmbedekte tablette).

SAMESTELLING:
Elke filmbedekte tablet bevat efavirens 600 mg, emtrisitabien 200 mg en tenofovir disoproksielfumaraat 300 mg. Suiker vry.

Ander bestanddele sluit mikrokristallyne sellulose, kroskarmellose natrium, hidroksipropielsellulose, natriumlourielsulfaat, magnesiumstearaat (plantaardig), gepregelatiniseerde stysel, polivinielalkohol, titaandioksied (C.I. 77891), poliëtileenglikol, talk, rooi ysteroksied (C.I. 77491) en swart ysteroksied (C.I. 77499) in.

WAARSKUWING
MELKSUURASIDOSE EN ERGE HEPATOMEGALIE MET STEATOSE, INSLUITENDE FATALE GEVALLE IS MET DIE GEBRUIK VAN NUKLEOSIEDANALOË, ALLEEN OF IN KOMBINASIE MET ANDER ANTIRETROVIRUSMIDDELS AANGEMELD (SIEN **WAARSKUWINGS EN SPESIALE VOORGSMAATREËLS**).
ERGE, AKUTE AGTERUITGANG VAN HEPATITIS B IS IN PASIËNTE AANGEMELD WAT MET DIE GEBRUIK VAN EMTRISITABIEN OF TENOFOVIR, WAT KOMPONENTE VAN **TRIOLAR TABLETS** IS, GESTAAK HET AANGEMELD. LEWERFUNKSIE BEHOORT NOUKEURIG GEMONITOR TE WORD MET BEIDE KLINIESE EN LABORATORIUMOPVOLG VIR TEN MINSTE ETLIKE MAANDE IN PASIËNTE WAT BEHANDELING MET **TRIOLAR TABLETS** STAAK EN MET BEIDE MIV EN HBV BESMET IS. INDIEN VAN TOEPASSING KAN INISIËRING VAN ANTIHEPATITIS B TERAPIE GEREGVERDIG WORD (SIEN **WAARSKUWINGS EN SPESIALE VOORSORGSMAATREELS**).

FARMAKOLOGIESE KLASSIFIKASIE:
A 20.2.8 Antimikrobiese (chemoterapeutiese) middels. Antivirusmiddels.

FARMAKOLOGIESE WERKING:
Farmakodinamiese eienskappe:
TRIOLAR TABLETS is 'n vastedosis kombinasietablet wat efavirens, emtrisitabien en tenofovir disoproksielfumaraat (tenofovir DF) bevat. Efavirens is 'n nie-nukleosied trutranskriptaseïnhibeerder; emtrisitabien is 'n sintetiese nukleosiedanaloog van sitidien en tenofovir DF word *in vivo* na tenofovir, 'n asikliese nukleosiedfosfonaat (nukleotied) analoog van adenosien 5'- monofosfaat omgeskakel.
Efavirens:
Efavirens is 'n nie-nukleosied trutranskriptaseïnhibeerder (NNTTI) van MIV-1. Die aktiwiteit van efavirens word hoofsaaklik deur nie-kompeterende inhibisie van MIV-1 trutranskriptase (TT) gemedieer. Efavirens inhibeer nie MIV-2 en menslike sellulêre DNA-polimerase α, β, γ en δ nie.
Emtrisitabien:
Emtrisitabien, 'n NTTI, is 'n sintetiese nukleosiedanaloog van sitidien. Sellulêre ensieme fosforileer emtrisitabien na emtrisitabien-5'-trifosfaat. Emtrisitabien- 5'-trifosfaat kompeteer met die natuurlike substraat, deoksisitidien-5'-trifosfaat en word in die groeiende virus DNA geïnkorporeer wat tot terminasie van die ketting lei. Emtrisitabien-5'-trifosfaat toon swak inhibisie van soogdier DNA-polimerases α, β, ε en mitochondriale DNA polimerase γ.
Tenofovir disoproksielfumaraat:
Tenofovir DF, 'n NTTI, is 'n asikliese nukleosiedfosfonaat diësteranaloog van adenosienmonofosfaat en benodig aanvanklike diësterhidrolise vir omskakeling na tenofovir en daaropvolgende fosforilerings deur sellulêre ensieme om tenofovirdifosfaat te vorm. Tenofovirdifosfaat inhibeer die aktiwiteit van MIV-1 TT deur met die natuurlike substraat deoksiadenosien-5'-trifosfaat te kompeteer. Na inkorporering in DNA, word die DNA-ketting getermineer. Tenofovirdifosfaat toon swak inhibisie teen soogdier polimerases α, β en mitochondriale DNA-polimerase γ.

Antivirusaktiwiteit:
Efavirens, emtrisitabien en tenofovir disoproksielfumaraat:
In kombinasiestudies wat die antivirusaktiwiteit *in vitro* van emtrisitabien en efavirens saam, efavirens en tenofovir saam en emtrisitabien en tenofovir saam geëvalueer het, is bykomstige tot sinergistiese antiviruseffekte waargeneem.

Weerstand:
Efavirens, emtrisitabien en tenofovir disoproksielfumaraat:
MIV-isolate met verminderde vatbaarheid vir die emtrisitabien en tenofovir-kombinasie is *in vitro* geselekteer.
Na genotipiese ontleding is die M184V/I en/of K65R aminosuurvervangings in die virus TT geïdentifiseer.
Efavirens:
Kliniese isolate met verminderde vatbaarheid *in vitro* teen efavirens is verkry. Die mees dikwels waargenome aminosuurvervanging wat in kliniese studies met efavirens waargeneem is, is K103N (54 %). Een of meer TT-vervangings by aminosuurposisies 98, 100, 101, 103, 106, 108, 188, 190, 225, 227 en 230 is waargeneem in pasiënte in wie die behandeling met efavirens in kombinasie met ander antiretrovirusmiddels misluk het. Ander weerstandige mutasies wat dikwels ontwikkel sluit L100I (7 %), K101E/Q/R (14 %), V108I (11 %), G190S/T/A (7 %), P225H (18 %) en M230I/L (11 %) in.
MIV-isolate met verminderde vatbaarheid vir efavirens (meer as 230-voudige toename in EK_{90} waarde) het vinnig onder seleksie *in vitro* ontwikkel. Genotipiese karakterisering van hierdie virusse het mutasies geïdentifiseer wat tot enkel aminosuurvervangings L100I of V179D, dubbel vervangings L100I/V108I en driedubbel vervangings L100I/V179D/Y181C in TT gelei het.
Emtrisitabien:
MIV-isolate wat weerstand teen emtrisitabien bied is *in vitro* geselekteer. Genotipiese onteding van hierdie isolate het aangetoon dat 'n afname in die vatbaarheid teen emtrisitabien met 'n mutasie in die MIV TT-geen by kodon 184 geassosieer is. Hierdie mutasie het 'n aminosuurvervanging van metionien deur valien of isoleusien (M184V/I) veroorsaak.
Tenofovir disoproksielfumaraat:
Isolate van MIV-1 wat verminderde vatbaarheid vir tenofovir getoon het is *in vitro* geselekteer. Hierdie virusse het 'n K65R mutasie in trutranskriptase aangetoon en 'n 2- tot 4-voudige afname in vatbaarheid teen tenofovir getoon.

Kruisweerstand:
Efavirens, emtrisitabien en tenofovir disoproksielfumaraat:
Kruisweerstand is onder NNTTIs uitgewys. Dit is ook bekend dat kruisweerstand onder sekere NTTIs kan ontwikkel. Die M184V/I en/of K65R vervangings wat *in vitro* deur die kombinasie van emtrisitabien en tenofovir geselekteer is, is ook in sommige MIV-1 stamme uit individue in wie die behandeling met tenofovir in kombinasie met lamivudien of emtrisitabien, en abasavir of didanosien misluk het, waargeneem. Kruisweerstand onder hierdie middels kan daarom in pasiënte wie se virus een of beide van hierdie aminosuurvervangings herberg, ontwikkel.

Farmakokinetiese eienskappe:
Efavirens:
Absorpsie:
Piek plasmakonsentrasies van efavirens van 1,6 - 9,1 µM is na 5 ure na 'n enkel dosering van 100 mg tot 1600 mg aan onbesmette vrywilligers bereik. Alhoewel dosisverwante toenames in K_{maks} en AOK waargeneem is vir dosisse van tot soveel as 1600 mg, is hierdie toenames kleiner as proporsioneel, wat op 'n afname in absorpsie teen hoër dosisse dui. Plato plasmakonsentrasies word na 6 tot 10 dae bereik.
Verspreiding:
Efavirens is hoogs proteïengebonde (ongeveer 99,5 % tot 99,75 %), hoofsaaklik aan albumien. Konsentrasies in die serebrospinale vloeistof het met 0,26 tot 1,19 % (gemiddeld 0,69 %) van die ooreenstemmende plasmakonsentrasies in MIV-1 besmette individue, aan wie 200 tot 600 mg efavirens een keer per dag vir ten minste een maand toegedien is, gewissel. Dit is ongeveer drie keer meer as die nie-proteïengebonde (vry) fraksie van efavirens in plasma.
Metabolisme:
Efavirens word hoofsaaklik deur die sitochroom P450 sisteem na gehidroksileerde metaboliete gemetaboliseer met daaropvolgende glukuronidasie van hierdie gehidroksileerde metaboliete. Die metaboliete is nie teen MIV-1 aktief nie. CYP3A4 en CYP2B6 is die belangrikste isoënsieme wat in die metabolisme van efavirens betrokke is. Efavirens, deur induksie van P450 ensieme, induseer sy eie metabolisme.
Eliminasie:
Efavirens besit 'n lang terminale halfleeftyd van 52 - 76 ure en 40 - 50 ure na enkel en veelvuldige dosisse, respektiewelik. Na die toediening van 'n radiogemerkte dosis, is 14 - 34 % van efavirens in die urien (hoofsaaklik as metaboliete) en 16 - 61 % in die feses herwin (hoofsaaklik as moedermiddel).

Emtrisitabien:
Die farmakokinetiese eienskappe van emtrisitabien word in tabel 1 opgesom.
Absorpsie:
Na orale toediening van emtrisitabien (200 mg) word emtrisitabien vinnig geabsorbeer met piek plasmakonsentrasies wat 1 - 2 ure na dosering voorkom.
Verspreiding:
In vitro binding van emtrisitabien aan menslike plasmaproteïene is < 4 % en is afhanklik van die konsentrasie in die reikwydte van 0,02 - 200 µg/mℓ.
Metabolisme en eliminasie:
Na die toediening van radiogemerkte emtrisitabien word ongeveer 86 % in die urien en 13 % as metaboliete herwin. Die metaboliete van emtrisitabien sluit 3'-sulfoksied diastereomere en hul glukuronsuur konjugaat in. Emtrisitabien word deur 'n kombinasie van glomerulêre filtrasie en aktiewe buissekresie geëlimineer. Na 'n enkel dosis emtrisitabien (200 mg) is die plasmahalfleeftyd van emtrisitabien ongeveer 10 ure.

Tenofovir disoproksielfumaraat:
Die farmakokinetiese eienskappe van tenofovir disoproksielfumaraat word in tabel 2 opgesom.
Absorpsie:
Na orale toediening van tenofovir, word maksimum tenofovir serumkonsentrasies na 1,0 ± 0,4 ure bereik.
Verspreiding:
Die *in vitro* binding van tenofovir aan menslike plasmaproteïene (< 0,7 %) is onafhanklik van die konsentrasie oor die reikwydte van 0,01 - 25 µg/mℓ.
Metabolisme en eliminasie:
Ongeveer 70 - 80 % van die intraveneuse dosis van tenofovir word onveranderd in die urien herwin. Tenofovir word deur 'n kombinasie van glomerulêre filtrasie en aktiewe buissekresie geëlimineer. Na 'n enkel dosis tenofovir, is die terminale halfleeftyd van tenofovir ongeveer 17 ure.

Tabel 1: Enkel dosis farmakokinetiese parameters vir emtrisitabien en tenofovir in volwassenes[1]

	Emtrisitabien	Tenofovir
Vastende Orale biobeskikbaarheid[2] (%)	92 (83,1 - 106,4)	25 (NB - 45,0)
Plasma Terminale eliminasiehalfleeftyd[2] (ure)	10 (7,4 - 18,)	17 (12,0 - 25,7)
K_{maks}[3] (µg/ml)	1,8 ± 0,72[4]	0,30 ± 0,09
AOK[3] (µg.uur/ml)	10,0 ± 3,12[4]	2,29 ±0,69
CL/F[3] (ml/min)	302 ± 94	1043 ± 115
CL_{nier}[3] (ml/min	302 ± 89	243 ± 33

[1] NB = Nie bereken nie
[2] Mediaan (reikwydte)
[3] Gemiddeld (± SA)
[4] Data aangebied as platowaardes

Effekte van voedsel op orale absorpsie:
TRIOLAR TABLETS is nie in die teenwoordigheid van voedsel geëvalueer nie. Die toediening van efavirens tablette met 'n hoë vet maaltyd het die gemiddelde AOK en K_{maks} van efavirens met 28 % en 79 % respektiewelik, verhoog in vergelyking met toediening in die vastende staat. In vergelyking met vastende toediening het die dosering van tenofovir DF en emtrisitabien in kombinasie met hoë vet maaltyd of 'n ligte maaltyd die gemiddelde AOK en K_{maks} van tenofovir met 35 % en 15 % respektiewelik verhoog, sonder om die blootstelling aan emtrisitabien te beïnvloed.

Spesiale populasies:
Pediatriese en bejaarde pasiënte:
Farmakokinetiese studies met tenofovir DF is nie in pediatriese pasiënte (jonger as 18 jaar oud) uitgevoer nie. Efavirens is nie in pediatriese pasiënte jonger as 3 jaar oud of wat minder as 13 kg weeg, uitgevoer nie. Emtrisitabien is in pediatriese pasiënte vanaf 3 maande tot 17 jaar oud uitgevoer. **TRIOLAR TABLETS** word nie vir pediatriese toediening aanbeveel nie. Die farmakokinetika van efavirens, emtrisitabien en tenofovir is nie volledig in bejaardes (ouer as 65 jaar) geëvalueer nie (sien **WAARSKUWINGS EN SPESIALE VOORSORGSMAATREËLS**).

Pasiënte met ingekorte nierfunksie:
Efavirens:
Die farmakokinetika van efavirens is nie in pasiënte met ingekorte nierfunksie bestudeer nie; minder as 1 % van efavirens word egter onveranderd deur die niere uitgeskei. Daarom, behoort die impak van ingekorte nierfunksie op die eliminasie van efavirens minimaal te wees.
Emtrisitabien en tenofovir disoproksielfumaraat:
Die farmakokinetika van emtrisitabien en tenofovir DF word in pasiënte met ingekorte nierfunksie verander. In pasiënte met 'n kreatinienopruiming van minder as 50 mℓ/min het die K_{maks} en $AOK_{0-\infty}$ van emtrisitabien en tenofovir toegeneem (sien **KONTRA-INDIKASIES, WAARSKUWINGS EN SPESIALE VOORSORGSMAATREËLS, Ingekorte nierfunksie**).

Pasiënte met ingekorte lewerfunksie:
Efavirens:
Die farmakokinetika van efavirens is nie voldoende in pasiënte met ingekorte lewerfunksie bestudeer nie (sien **WAARSKUWINGS EN SPESIALE VOORSORGSMAATREËLS**).
Emtrisitabien:
Die farmakokinetika van efavirens is nie voldoende in pasiënte met ingekorte lewerfunksie bestudeer nie. Emtrisitabien word egter nie beduidend deur lewerensieme gemetaboliseer nie. Daarom behoort die impak van ingekorte lewerfunksie beperk te wees.
Tenofovir disoproksielfumaraat:
Die farmakokinetika van tenofovir na 'n dosis van 300 mg tenofovir DF is in nie-MIV besmette pasiënte met matig tot erg ingekorte lewerfunksie bestudeer. Daar was geen noemenswaardige verandering in die farmakokinetika van tenofovir in pasiënte met ingekorte lewerfunksie in vergelyking met pasiënte met normale lewerfunksie nie.

INDIKASIES:
TRIOLAR TABLETS word aangedui as enkel of kombinasieterapie vir MIV-1 infeksie in volwassenes.

KONTRA-INDIKASIES:
TRIOLAR TABLETS word teenaangedui in pasiënte:
- Met voorheen aangetoonde hipersensitiwiteit teen emtrisitabien, tenofovir of efavirens of enige ander van die komponente van die produk.
- Met matig tot erg ingekorte nierfunksie (kreatinienopruiming < 50 mℓ/min (sien **WAARSKUWINGS EN SPESIALE VOORSORGSMAATREËLS** en **DOSIS EN GEBRUIKS-AANWYSINGS**).
- Wat huidiglik behandeling met astemisool, kisapried, midasolam, triasolam of ergotderivate ontvang, aangesien kompetisie vir CYP 3A4 deur die efavirens in **TRIOLAR TABLETS** tot inhibisie van die metabolisme van hierdie medisyne kan lei, asook die potensiaal vir ernstige en/of lewensbedreigende newe-effekte (bv. hartdisritmieë, verlengde sedering of respiratoriese onderdrukking) kan ontwikkel.
- Pasiënte wat huidiglik vorikonasool gebruik, aangesien efavirens die plasmakonsentrasie van vorikonasool beduidend laat afneem, terwyl vorikonasool die plasmakonsentrasie van efavirens aansienlik laat toeneem. Aangesien **TRIOLAR TABLETS** 'n vaste dosis kombinasieproduk is, kan die dosis van efavirens nie verander word nie. Daarom behoort vorikonasool en **TRIOLAR TABLETS** nie saam toegedien te word nie.
- Wat swanger is of borsvoed (sien **SWANGERSKAP EN LAKTASIE**).

WAARSKUWINGS EN SPESIALE VOORSORGSMAATREËLS:
Melksuurasidose/hiperlaktatemie:
Die gebruik van **TRIOLAR TABLETS** kan weens mitochondriale wanfunksie tot potensieel fatale melksuurasidose lei.
Kliniese eienskappe is nie-spesifiek en sluit naarheid, braking, buikpyn, dispnee, moegheid en massaverlies in.
In pasiënte met verdagte simptome of biochemie, behoort die veneuse laktaatvlak (normaal <2 mmol/ℓ) en serumbikarbonaat gemeet en as volg opgetree te word.
- **Laktaat 2 - 5 mmol/ℓ met minimum simptome:** Skakel oor na middels wat minder waarskynlik melksuurasidose sal veroorsaak.
- **Laktaat 5 - 10 mmol/ℓ met simptome en/of laer bikarbonaat:** Staak NTTIs en verander die behandeling. Wanneer die laktaatvlak gestabiliseer het, gebruik medisyne wat minder waarskynlik melksuurasidose sal veroorsaak. Sluit ander oorsake uit (bv. sepsis, uremie, diabetiese ketoasidose, tirotoksikose en hipertiroïedisme).
- **Laktaat > 10 mmol/ℓ: STAAK alle terapie** (80 % mortaliteit).

Die bogenoemde laktaatvlakke is moontlik nie in pediaters van toepassing nie.
Sorg behoort aan die dag gelê te word wanneer **TRIOLAR TABLETS** aan pasiënte met bekende faktore vir lewersiekte toegedien word.
Behandeling met **TRIOLAR TABLETS** behoort opgeskort te word in enige pasiënt wat kliniese of laboratorium bevindings ontwikkel wat op melksuurasidose of hepatotoksisiteit dui.

Mitochondriale disfunksie:
Daar is *in vitro* en *in vivo* aangetoon dat nukleosied- en nukleotiedanaloë 'n wisselende graad van mitochondriale beskadiging veroorsaak. Daar bestaan vermeldings van mitochondriale disfunksie in MIV-negatiewe babas wat *in utero* en/of post-nataal aan nukleosiedanaloë blootgestel is. Behalwe vir melksuurasidose/hiperlaktatemie (sien hierbo) sluit ander manifesterings van mitochondriale disfunksie hematologiese afwykings (anemie, neutropenie) en perifere neuropatie in. Sommige neurologiese afwykings wat eers later ontwikkel is aangemeld (hipertonie, stuipaanvalle, abnormale gedrag). Dit is nie bekend of die neurologiese afwykings van verbygaande aard of permanent is nie. Enige fetus wat *in utero* aan nukleosied- en nukleotiedanaloë blootgestel is, selfs MIV-negatiewe babas/kinders, behoort kliniese en laboratoriumopvolg te ondergaan en behoort in die geval van relevante tekens of simptome ten volle vir mitochondriale disfunksie ondersoek te word.

Pankreatitis:
Pankreatitis is in sommige pasiënte wat **TRIOLAR TABLETS** ontvang, waargeneem.
Pankreatitis moet oorweeg word wanneer 'n pasiënt buikpyn, naarheid, braking of verhoogde biochemiese merkers ontwikkel. Staak die gebruik van **TRIOLAR TABLETS** totdat 'n diagnose van pankreatitis uitgesluit is.

Lewersiekte:
Weens nie-alkoholiese vetlewersiekte (lewersteatose) kan die gebruik van **TRIOLAR TABLETS** tot hepatomegalie lei. Die veiligheid en effektiwiteit van **TRIOLAR TABLETS** is nie in pasiënte met beduidende onderliggende lewerafwykings/-siekte vasgestel nie. In die geval van meegaande antivirusterapie vir hepatitis B of C, moet die relevante voubiljette vir hierdie medisyne geraadpleeg word.
Pasiënte met reeds bestaande lewerdisfunksie, insluitende chroniese, aktiewe hepatitis toon 'n toename in die frekwensie van lewerfunksie-abnormaliteite gedurende kombinasie antiretrovirusterapie en behoort gemonitor te word. As daar bewys van agteruitgang van die lewersiekte in sulke pasiënte is, behoort tydelike of permanente staking van behandeling oorweeg te word.

Pasiënte met beide MIV en hepatitis B of C infeksie:
Pasiënte met chroniese hepatitis B of C en wat met antiretrovirus terapie behandel word, het 'n groter risiko vir erge en potensieel fatale newe-effekte van die lewer.
Mediese praktisyns behoort na die huidige MIV-behandelingsriglyne te verwys vir die optimale bestuur van MIV-infeksie in pasiënte wat ook met hepatitis B of C (HBV) besmet is.
In die geval van meegaande antivirusterapie, moet ook na die relevante voubiljette vir hierdie medisyne verwys word.
Pasiënte wat met beide MIV en HBV besmet is en wat met die gebruik van **TRIOLAR TABLETS** staak, behoort noukeurig met beide kliniese en laboratoriumopvolg na staking van die terapie opgevolg te word. In pasiënte met gevorderde lewersiekte of -sirrose, word die staking van terapie nie aanbeveel nie, aangesien die agteruitgang van hepatitis na behandeling tot lewerdekompensering kan lei.
Die staking van **TRIOLAR TABLETS** in pasiënte wat met beide MIV en HBV besmet is, kan met erge agteruitgang van hepatitis geassosieer word.

Medetoediening saam met verwante medisyne:
Verwante medisyne wat nie saam met **TRIOLAR TABLETS** toegedien moet word nie sluit emtrisitabien, tenofovir DF, emtrisitabien/tenofovir DF en efavirens in, wat dieselfde aktiewe bestanddele as **TRIOLAR TABLETS** besit. Weens ooreenkomste tussen emtrisitabien en lamivudien, behoort **TRIOLAR TABLETS** nie saam met medisyne wat lamivudien bevat, insluitende lamivudien/sidovudien, lamivudien en abasavir toegedien te word nie.

Ingekorte nierfunksie:
Emtrisitabien en tenofovir, twee van die bestanddele van **TRIOLAR TABLETS**, word hoofsaaklik deur die niere uitgeskei. **TRIOLAR TABLETS** behoort nie aan pasiënte met 'n kreatinienopruiming < 50 mℓ/min toegedien te word nie.
Daar bestaan vermeldings van ingekorte nierfunksie, insluitende gevalle van akuut ingekorte nierfunksie en Fanconi se sindroom (nierbuisbeskadiging met erge hipofosfatemie) wat met die gebruik van tenofovir DF geassosieer word (sien **NEWE-EFFEKTE**).
Daar word aanbeveel dat kreatinienopruiming in alle pasiënte vóór inisiëring van, en ook waar klinies van toepassing gedurende die terapie met **TRIOLAR TABLETS** bereken word. Roetine monitering van berekende kreatinienopruiming en serumkalium behoort in pasiënte met 'n risiko vir ingekorte nierfunksie uitgevoer te word.
Die gebruik van **TRIOLAR TABLETS** behoort vermy te word in pasiënte wat terselfdertyd of onlangs 'n nefrotoksiese middel gebruik of gebruik het.

Interaksies met atasanavir en ander medisyne (sien **INTERAKSIES**).
Die gelyktydige gebruik van **TRIOLAR TABLETS** saam met St. John se kruid (*Hypericum perforatum*) of produkte wat St. John se kruid bevat, word nie aanbeveel nie. Daar word verwag dat die medetoediening van NNTTI, insluitende efavirens, die NNTTI konsentrasies aansienlik sal verminder en sub-optimale vlakke van efavirens veroorsaak wat tot 'n verlies aan virologiese respons en moontlike weerstand teen die NNTTI klas kan lei.

Psigiatriese simptome:
Ernstige psigiatriese newe-effekte is in pasiënte wat met efavirens behandel is, aangemeld. In gekontroleerde studies van pasiënte wat met regimens wat efavirens bevat behandel is, was die frekwensie van spesifieke ernstige psigiatriese episodes onder pasiënte wat efavirens of die kontroleregimens, respektiewelik ontvang het: Erge depressie (2,4 %, 0,9 %), selfmoordidees (0,7 %, 0,3 %), nie-fatale selfmoordpogings (0,5 %, 0 %), aggressiewe gedrag (0,4 %, 0,5 %), paranoïese gedagtes (0,4 %, 0,3 %) en maniese gedagtes (0,2 %, 0,3 %). Wanneer psigiatriese simptome soortgelyk aan dié hierbo genoem, gekombineer is en as 'n groep in 'n multifaktoriale analise van data geëvalueer is, is die behandeling met efavirens met 'n toename in die voorkoms van hierdie psigiatriese simptome geassosieer. Ander faktore wat met 'n toename in die voorkoms van hierdie psigiatriese simptome geassosieer word, is 'n geskiedenis van inspuitbare dwelmgebruik, psigiatriese geskiedenis en ontvangs van psigiatriese medikasie met aanvangs van die studie; soortgelyke verwantskappe is in beide die efavirens en kontrole behandelingsgroepe waargeneem.
Een persent van die efavirens behandelde indiwidue het weens een of meer van hierdie geselekteerde psigiatriese simptome die behandeling gestaak of onderbreek. Daar bestaan ook nabemarkingsvermeldings van dood deur selfmoord, delusies en psigoseagtige gedrag. 'n Oorsaaklike verwantskap met die gebruik van efavirens kan egter nie uit hierdie vermeldings vasgestel word nie. Pasiënte met ernstige psigiatriese newe-effekte behoort onmiddellik mediese evaluering te ondergaan om vas te stel of die risiko van voortgesette behandeling swaarder as die voordele weeg (sien **NEWE-EFFEKTE**).

Simptome van die senuweestelsel:
53 % van die pasiënte wat efavirens in gekontroleerde studies ontvang het, het simptome van die senuweestelsel aangemeld teenoor 25% van die pasiënte wat kontrole regimens ontvang het. Hierdie simptome het duiseligheid (28,1 %), slaaploosheid (16,3 %) ingekorte konsentrasievermoë (8,3 %), slaapsug (7,0 %), abnormale drome (6,2 %) en hallusinasies (1,2 %) ingesluit. Ander aangemelde simptome het euforie, verwardheid, agitasie amnesie, beneweling, abnormale denke en depersonalisering ingesluit. Die meerderheid van hierdie simptome was gering tot matig van aard (50,7 %). Simptome was erg in 2,0 % van gevalle. Oor die algemeen het 2,1 % van die indiwidue die terapie as gevolg hiervan gestaak. Hierdie simptome begin gewoonlik gedurende die eerste of tweede dag van terapie en verdwyn gewoonlik na die eerste 2 - 4 weke van terapie. Na 4 weke van terapie het die voorkoms van simptome van die senuweestelsel van ten minste matige aard tussen 5 % en 9 % gewissel in individue wat met 'n kontroleregimen behandel is. Pasiënte behoort ingelig te word dat hierdie algemene simptome waarskynlik met voortgesette terapie sal verbeter en nie die aanvangs van minder dikwels voorkomende psigiatriese simptome voorspel nie. Dosering met slapenstyd kan die verdraagsaamheid van hierdie simptome van die senuweestelsel verbeter.
Pasiënte wat **TRIOLAR TABLETS** ontvang behoort gewaarsku te word teen die potensiaal vir bykomende simptome van die sentrale senuweestelsel wanneer **TRIOLAR TABLETS** saam met alkohol of psigoaktiewe medisyne geneem word.
Pasiënte wat simptome van die sentrale senuweestelsel soos duiseligheid, ingekorte konsentrasie en/of lomerigheid ondervind, potensieel gevaarlike take soos bestuur of met masjinerie te werk, behoort te vermy.
Daar bestaan vermeldings van senuweestelselsimptome met die gebruik van efavirens (sien **NEWE-EFFEKTE**). Boonop is psigoseagtige reaksies, insluitende delusies en ontoepaslike gedrag (insluitende aggressiewe reaksies) ook aangemeld. Hierdie reaksies het hoofsaaklik in pasiënte met 'n geskiedenis van geestelike siekte of middelmisbruik voorgekom. Daar bestaan 'n paar vermeldings van erge akute depressie (insluitende selfmoordidees/-pogings) in beide efavirens- en kontrolebehandelde pasiënte, hoofsaaklik in pasiënte met 'n vorige geskiedenis van depressie. Pasiënte behoort aangeraai te word om onmiddellik hul dokter te raadpleeg as hulle hierdie simptome ondervind aangesien die gebruik van **TRIOLAR TABLETS** moontlik gestaak moet word.

Veluitslag:
Geringe tot matige uitslag wat gewoonlik met volgehoue behandeling verdwyn, is met die gebruik van efavirens waargeneem. Die behandeling met toepaslike antihistamiene en/of kortikosteroïede kan die verdraagsaamheid verbeter en die verdwyning van simptome versnel. Behandeling met **TRIOLAR TABLETS** behoort gestaak te word in pasiënte wat erge uitslag met blasies, afskilfering, slymvliesbetrokkenheid of koors ondervind.

Stuipaanvalle:
Stuipaanvalle is in pasiënte wat efavirens ontvang waargeneem, hoofsaaklik in dié met 'n bekende geskiedenis van stuipaanvalle.
Pasiënte wat terselfdertyd antistuip medikasies wat hoofsaaklik deur die lewer gemetaboliseer word ontvang, soos fenitoïen en fenobarbital, mag periodieke monitering van plasmavlakke vereis.

Cholesterol:
Die monitering van cholesterol- en trigliseriedvlakke behoort in pasiënte wat met **TRIOLAR TABLETS** behandel word, oorweeg te word (sien **NEWE-EFFEKTE**).

Beeneffekte:
TRIOLAR TABLETS verminder die beenmineraaldigtheid. Beenmonitering behoort in MIV-besmette pasiënte met 'n geskiedenis van patologiese beenfrakture of 'n risiko van osteopenie, oorweeg te word. Alhoewel die effek van supplementering van kalsium en vitamien D nie bestudeer is nie, kan die supplementering vir alle pasiënte van voordeel wees. Indien beenabnormaliteite vermoed word, behoort 'n toepaslike konsultasie verkry te word.

Lipodistrofie en metaboliese abnormaliteite:
Kombinasie antiretrovirusterapie is met die herverspreiding/akkumulasie van liggaamsvet, insluitende sentrale vetsug, dorsoservikale vetvergroting (buffelskof), perifere vermaering, gesigsvermaering, borsvergroting en verhoogde serumlipied- en glukosevlakke in MIV-pasiënte geassosieer. 'n Kliniese ondersoek behoort die evaluering van fisiese tekens van die herverspreiding van vet in te sluit. Pasiënte met bewys van lipodistrofie behoort 'n deeglike kardiovaskulêre risiko-evaluering te ondergaan.

Immuunherinstelling en inflammatoriese sindroom:
Immuunherinstelling en inflammatoriese sindroom (IRIS) is 'n immunopatologiese respons wat volg op die vinnige herstel van patogeenspesifieke immuunresponse tot reeds bestaande immuun-disregulering wat kort na die begin van kombinasie antiretrovirusterapie (kART) voorkom. Dit presenteer tipies met paradoksale agteruitgang van opportunistiese infeksies wat behandel word of met ontmaskering van 'n asimptomatiese opportunistiese infeksie, dikwels met 'n atipiese inflammatoriese presentering. IRIS ontwikkel gewoonlik binne die eerste drie maande na inisiëring van ART en kom meer dikwels in pasiënte met lae CD4 tellings voor. Algemene voorbeelde van IRIS reaksies teen opportunistiese siektes is tuberkulose, sitomegalovirusretinitis en kriptokokmeningitis. Toepaslike behandeling van die opportunistiese siekte behoort ingestel en voortgesit te word en ART behoort ook voortgesit te word. Inflammatoriese manifesterings verdwyn gewoonlik na 'n paar weke. Erge gevalle mag op kortikosteroïede reageer, maar daar is slegs beperkte bewys hiervan in pasiënte met tuberkulose IRIS. Outo-immuunafwykings (soos Graves se siekte) is ook as IRIS reaksies aangemeld. Die aangemelde tyd tot aanvangs wissel egter meer en hierdie episodes kan 'n aantal maande na aanvangs van behandeling voorkom.

Osteonekrose:
Alhoewel die etiologie as multifaktoriaal beskou word (insluitende die gebruik van kortikosteroïede, alkoholinname, erge immuunonderdrukking en hoër liggaamsmassa-indeks), is gevalle van osteonekrose aangemeld, veral in pasiënte met gevorderde MIV-siekte en/of langtermyn blootstelling aan kombinasie antiretrovirusterapie (kART). Pasiënte behoort aangeraai te word om mediese advies in te win wanneer hulle gewrigspyn, gewrigstyfheid of moeite met beweging ondervind.

Opportunistiese infeksies:
Pasiënte wat **TRIOLAR TABLETS** ontvang behoort daaroor ingelig te word dat hulle mag voortgaan om opportunistiese infeksies en ander komplikasies van MIV-siekte op te doen en behoort daarom onder noukeurige waarneming deur professionele gesondheidswerkers met ondervinding in die behandeling van pasiënte met verwante MIV-siekte gehou te word. Die viruslading en CD4 tellings behoort gereeld gemonitor te word.

Die risiko van oordraging van MIV na ander:
Pasiënte behoort in kennis gestel te word dat die huidige antiretrovirusterapie, insluitende **TRIOLAR TABLETS**, nie die risiko van oordraging van MIV na ander deur seksuele kontak of bloedkontaminasie verminder nie. Toepaslike voorsorgsmaatreëls behoort getref te word.

Pediatriese gebruik:
Die veiligheid en effektiwiteit van **TRIOLAR TABLETS** is nie in kinders vasgestel nie.

Gebruik in bejaardes:
Kliniese studies van vastedosis kombinasies van emtrisitabien en tenofovir, soos in **TRIOLAR TABLETS**, het nie genoeg individue van ouer as 65 jaar ingesluit om vas te stel of hulle anders as jonger individue reageer nie. Oor die algemeen behoort sorg aan die dag gelê te word wanneer dosisse vir bejaarde pasiënte geselekteer word. Die groter frekwensie van 'n afname in lewer-, nier- en hartfunksie, asook meegaande siekte of medisinale terapie, behoort in gedagte gehou te word.

Effek op die vermoë om te bestuur of met masjinerie te werk:
TRIOLAR TABLETS kan tot duiseligheid, ingekorte konsentrasievermoë en/of lomerigheid lei. Pasiënte behoort aangeraai te word dat wanneer hulle hierdie simptome ontwikkel, hulle potensieel gevaarlike take soos om te bestuur en met masjinerie te werk, moet vermy.

INTERAKSIES:
Efavirens:
In vivo is daar aangetoon dat efavirens CYP3A4 induseer. Ander middels wat substrate van CYP3A4 is, mag laer plasmakonsentrasies toon wanneer hulle saam met efavirens toegedien word. *In vitro* studies het aangetoon dat efavirens 2C9, 2C19 en 3A4 isoënsieme in die reikwydte van waargenome plasmakonsentrasies van efavirens inhibeer. Die medetoediening van efavirens saam met medisyne wat hoofsaaklik deur hierdie ensieme gemetaboliseer word, kan tot veranderde plasmakonsentrasies van die medetoegediende medisyne lei.
Daar word verwag dat medisyne wat CYP3A4 aktiwiteit induseer (bv. fenobarbital, rifampien, rifabutien), die opruiming van efavirens sal verhoog, wat tot laer plasmakonsentrasies sal lei.
Emtrisitabien en tenofovir disoproksielfumaraat:
Aangesien emtrisitabien en tenofovir hoofsaaklik deur die niere uitgeskei word, kan die medetoediening van **TRIOLAR TABLETS** saam met middels wat nierfunksie vertraag of vir aktiewe buissekresie kompeteer, die serumkonsentrasies van emtrisitabien, tenofovir en/of ander middels wat deur die niere uitgeskei word, verhoog. Sommige voorbeelde sluit toasiklovir, adefovirdipivoksiel, sidofovir, gansiklovir, valasiklovir en valgansiklovir in, maar is nie tot hierdie middels beperk nie.
Die medetoediening van tenofovir DF en didanosien behoort met sorg onderneem te word en pasiënte wat hierdie kombinasie ontvang, behoort noukeurig vir didanosienverwante newe-effekte gemonitor te word. Didanosien behoort gestaak te word in pasiënte wat didanosienverwante newe-effekte ontwikkel (vir aanbevelings oor doseringsaanpassings vir didanosien, verwys na Tabel 3).
Onderdrukking van die CD4 tellings is in pasiënte wat tenofovir DF saam met didanosien 400 mg daagliks ontvang, waargeneem.
Daar is aangetoon dat atasanavir en lopinavir/ritonavir die konsentrasies van tenofovir verhoog. Die meganisme van hierdie interaksie is nie bekend nie. Hoër tenofovir konsentrasies kan moontlik tenofovirverwante newe-effekte, insluitende nierafwykings, potensieer. Pasiënte wat atasanavir of lopinavir/ritonavir saam met tenofovir ontvang, behoort vir tenofovirverwante newe-effekte gemonitor te word. **TRIOLAR TABLETS** behoort gestaak te word in pasiënte wat tenofovirverwante newe-effekte ontwikkel (vir aanbevelings oor doseringsaanpassings vir didanosien, verwys na Tabel 3).
Ander belangrike inligting oor medisyne interaksies vir **TRIOLAR TABLETS** word in tabel 2 en 3 opgesom. Die interaksies wat beskryf word is gebaseer op studies wat uitgevoer is met efavirens, emtrisitabien of tenofovir DF as indiwiduele middels, of is potensiële interaksies. Geen interaksiestudies is met die gebruik van **TRIOLAR TABLETS** uitgevoer nie.

Tabel 2: Medisyne wat teenaangedui is of wat nie vir gebruik saam met TRIOLAR TABLETS aanbeveel word nie.

Medisyneklas Naam van die medisyne	Kliniese kommentaar
Swamwerende middels: Vorikonasool	TEENAANGEDUI omdat efavirens die plasmakonsentrasies van vorikonasool aansienlik verminder en medetoediening kan die terapeutiese effektiwiteit van vorikonasool laat afneem. Vorikonasool laat die plasmakonsentrasies van efavirens aansienlik toeneem, wat op sy beurt die risiko van efavirensverwante newe-effekte laat toeneem.
Anti-migraine middels: Ergotderivate (dihidroërgotamien, ergonovien, ergotamien, metielergonovien)	TEENAANGEDUI weens die potensiaal vir ernstige en/of lewensbedreigende reaksies soos akute ergottoksisiteit wat deur perifere vasospasme en isgemie van die ledemate en ander weefsels gekenmerk word.
Antiretrovirusmiddels: Efavirens, emtrisitabien, tenofovir DF, lamivudien	Nie vir gebruik met **TRIOLAR TABLETS** nie aangesien die aktiewe bestanddele emtrisitabien, tenofovir en efavirens komponente van **TRIOLAR TABLETS** is. Lamivudien is soortgelyk aan emtrisitabien.
Bensodiasepiene: Midasolam, triasolam	TEENAANGEDUI weens die potensiaal vir lewensbedreigende reaksies soos verlengde sedering of 'n toename in sedering of respiratoriese onderdrukking.
Kalsiumkanaalblokkeerder: Bepridiel	TEENAANGEDUI weens die potensiaal vir ernstige en/of lewensbedreigende reaksies soos hartdisritmieë.
GI motiliteitsmedisyne: Kisapried	TEENAANGEDUI weens die potensiaal van ernstige en/of lewensbedreigende reaksies soos hartdisritmieë.
Neuroleptika: Pimosied	TEENAANGEDUI weens die potensiaal van ernstige en/of lewensbedreigende reaksies soos hartdisritmieë.
St. John se kruid (Hypericum perforatum)	WORD NIE AANBEVEEL NIE: Daar word verwag dat dit die plasmavlakke van efavirens beduidend verlaag: is nie in kombinasie met efavirens bestudeer nie.

Tabel 3:
Bevestigde en ander potensieel beduidende[1] middelinteraksies:
Verandering in dosis of regimen kan op grond van middelinteraksie-studies of voorspelde interaksies gebaseer word.

Meegaande medisyne Klas: Naam van die medisyne	Effek	Kliniese kommentaar
Antiretrovirusmiddels		
Proteaseïnhibeerder: Amprenavir	↓Amprenavir-konsentrasie	Efavirens besit die potensiaal om die serumkonsentrasies van amprenavir te verminder
Proteaseïnhibeerder: Fosamprenavirkalsium	↓Amprenavir-konsentrasie	Fosamprenavir (ongeskraag): Toepaslike dosisse van fosamprenavir en **TRIOLAR TABLETS** ten opsigte van veiligheid en effektiwiteit is nie vasgestel nie. Fosamprenavir/ritonavir: Addisionele 100 mg per dag (300 mg totaal) ritonavir word aanbeveel wanneer **TRIOLAR TABLETS** saam met fosamprenavir een keer per dag toegedien word. Geen verandering in die ritonavir dosis is nodig wanneer **TRIOLAR TABLETS** saam met fosamprenavir/ritonavir toegedien word nie. Geen verandering in die ritonavir dosis is nodig wanneer **TRIOLAR TABLETS** saam met fosamprenavir plus ritonavir twee keer per dag toegedien word nie.
Proteaseïnhibeerder: Atasanavir	↓ atasanavir konsentrasie ↑ tenofovir konsentrasie	Die plasmakonsentrasie van atasanavir is deur beide efavirens en tenofovir DF verminder. Daar is nie voldoende data beskikbaar om 'n dosisaanbeveling vir atasanavir of atasanavir/ritonavir saam met **TRIOLAR TABLETS** te maak nie. Daarom word die medetoediening van **TRIOLAR TABLETS** saam met atasanavir, weens besorgdheid oor die afname van die atasanavir konsentrasie, nie aanbeveel nie.
Protease ïnhibeerder: Indinavir	↓ indinavir konsentrasie	Die optimale indinavir dosis, wanneer in kombinasie met efavirens toegedien word, is nie bekend nie. Verhoging van die indinavir dosis na 1000 mg elke 8 ure kompenseer nie vir die toename in die metabolisme van indinavir weens efavirens nie.
Protease ïnhibeerder: Lopinavir/ritonavir	↓ lopinavir konsentrasie ↑ tenofovir konsentrasie	'n Toename in die dosis van lopinavir/ritonavir na 600/150 mg (3 tablette) twee keer per dag kan oorweeg word wanneer dit in kombinasie gebruik word met efavirens in pasiënte wat voorheen behandeling ontvang het en waar 'n afname in die vatbaarheid vir lopinavir klinies vermoed word. **Pasiënte behoort vir tenofovir verwante newe-effekte gemonitor te word. TRIOLAR TABLETS behoort in pasiënte wat tenofovir verwante newe-effekte ontwikkel, gestaak te word.**
Protease ïnhibeerder: Ritonavir	↑ ritonavir konsentrasie ↑ efavirens konsentrasie	Wanneer ritonavir 500 mg elke 12 ure saam met efavirens 600 mg een keer per dag toegedien word, word die kombinasie geassosieer met 'n hoër frekwensie van nadelige kliniese ondervindings (bv. duiseligheid, naarheid, parestesie), asook laboratoriumabnormaliteite (toename in lewerensieme). Monitering van lewerensieme word aanbeveel wanneer **TRIOLAR TABLETS** in kombinasie met ritonavir gebruik word.
Protease ïnhibeerder: Sakinavir	↑ sakinavir konsentrasie	Behoort nie as die enigste proteaseïnhibeerder saam met **TRIOLAR TABLETS** gebruik te word nie
NTTI: Didanosien	↑ didanosien konsentrasie	Hoër didanosien konsentrasies kan didanosienverwante newe-effekte potensieer, insluitende pankreatitis en neuropatie. **In pasiënte wat meer as 60 kg weeg behoort die didanosien dosis na 250 mg verlaag te word as dit saam met TRIOLAR TABLETS toegedien word. Daar is geen data beskikbaar om 'n dosis aanpassing van didanosien vir pasiënte wat minder as 60 kg weeg, aan te beveel nie.** Wanneer saam toegedien word, kan **TRIOLAR TABLETS** en didanosien onder vastende kondisies of met 'n ligte maaltyd (minder as 400 kkal, 20 % vet) geneem word. Die medetoediening van didanosien gebufferde formulasie saam met **TRIOLAR TABLETS** behoort onder vastende kondisies plaas te vind. **Die medetoediening van TRIOLAR TABLETS saam met didanosien behoort met sorg te geskied en pasiënte wat hierdie kombinasie ontvang, behoort noukeurig vir didanosienverwante newe-effekte gemonitor te word.**
Ander middels		
Teenstolmiddel: Warfarien	↑ of ↓ warfarien konsentrasie	Plasmakonsentrasies en effekte word potensieel verhoog of verlaag deur efavirens.
Antistuipmiddel: Karbamasepien	↓karbamasepien konsentrasie ↓efavirens konsentrasie	Daar bestaan nie genoeg data om dosis aanbeveling vir **TRIOLAR TABLETS** te maak nie. Alternatiewe antistuipbehandeling behoort gebruik te word
Fenitoïen Fenobarbital	↓antistuipmiddel konsentrasie ↓efavirens konsentrasie	Potensiaal vir afname in antistuip en/of efavirens plasmavlakke; periodieke monitering van antistuip plasmavlakke behoort uitgevoer te word.
Antidepressant: Sertralien	↓ sertralien konsentrasie	Toenames van die sertraliendosis behoort op grond van die kliniese respons gedoen te word.
Swamweerder: Itrakonasool Ketokonasool	↓ itrakonasool konsentrasie ↓ hidroksie-itrakonasool konsentrasie ↓ ketokonasool konsentrasie	Aangesien geen dosisaanpassing vir itrakonasool gemaak kan word nie, behoort alternatiewe swamwerende behandeling oorweeg te word. Middel interaksiestudies met **TRIOLAR TABLETS** en ketokonasool is nie uitgevoer nie. Efavirens besit die potensiaal om die plasmakonsentrasies van ketokonasool te verlaag
Anti-infektiewe middels: Klaritromisien	↓ klaritromisien konsentrasie ↑ 14-OH metaboliet konsentrasie	Die kliniese betekenis hiervan is onbekend. In onbesmette vrywilligers het 48 % egter uitslag ontwikkel terwyl hulle efavirens en klaritromisien ontvang het. Geen dosisaanpassing van **TRIOLAR TABLETS** word aanbeveel wanneer dit saam met klaritromisien toegedien word nie. Alternatiewe vir klaritromisien, soos asitromisien behoort oorweeg te word. Ander makroliede antibiotika soos eritromisien is nie in kombinasie met **TRIOLAR TABLETS** bestudeer nie.
Antimikobakteriële middels: Rifabutien	↓ rifabutien konsentrasie	Verhoog die daaglikse rifabutien dosis met 50 %. Oorweeg die verdubbeling van die rifabutien dosis in regimens war rifabutien twee of drie keer per week toegedien word.
Antimikobakteriële middels: Rifampisien	↓ efavirens konsentrasie	Die kliniese betekenis van 'n laer efavirens konsentrasie is nie bekend nie. Geen doseringsaanbevelings vir die gelyktydige gebruik van **TRIOLAR TABLETS** en rifampisien is vasgestel nie.
Kalsiumkanaalblokkeerders: Diltiasem	↓ diltiasem konsentrasie ↓ desasetiel-diltiasem konsentrasie	Dosering van diltiasem behoort op grond van die kliniese respons uitgevoer te word. Geen dosisaanpassing vir **TRIOLAR TABLETS** is nodig wanneer dit saam met diltiasem toegedien word nie.
Ander (bv. felodipien, nifedipien, nikardepien, verapamiel)	↓ N-monodes-metieldiltiasem konsentrasie ↓ kalsiumkanaal-blokkeerder	Daar bestaan geen data oor die potensiële interaksies met ander kalsiumkanaal-blokkeerders wat substrate vir CYP3A4 ensieme is nie. Daar bestaan 'n potensiaal vir die afname in plasmakonsentrasies van die kalsiumkanaalblokkeerder. Die dosis behoort op grond van die kliniese respons aangepas te word
HMG-KoA reduktase-inhibeerders: Atorvastatien, pravastatien, simvastatien	↓ atorvastatien konsentrasie ↓ pravastatien konsentrasie ↓ simvastatien konsentrasie	Die plasmakonsentrasies van atorvastatien, pravastatien en simvastatien het met efavirens afgeneem. Raadpleeg die volledige vou-biljette van die HMG-KoA reduktaseïnhibeerder vir riglyne oor individualisering van die dosis.
Narkotiese pynstiller: Metadoon	↓ metadoon konsentrasie	Die medetoediening van efavirens in MIV-1 besmette individue met 'n geskiedenis van inspuitbare medisyne gebruik het tot 'n afname in die plasmavlakke van metadoon en tekens van opiaatonttrekking gelei. Die metadoon dosis is met gemiddeld 22 % verhoog om die onttrekkingsimptome te verlig. Pasiënte behoort vir tekens van onttrekking gemonitor te word en hul metadoon dosis soos nodig verhoog te word om die simptome van onttrekking te verlig.
Orale voorbehoedmiddels: Etinielestradiol	↑ etinielestradiol konsentrasie	Die kliniese betekenis hiervan is nie bekend nie. Omdat die potensiële interaksie met orale voorbehoedmiddels nog nie ten volle gekenmerk is nie, behoort 'n betroubare vorm van skeidingskontrasepsie bykomend tot die orale voorbehoedmiddel gebruik te word.

[1] Hierdie tabel is nie allesinsluitend nie

Interferensie met efavirens bepaling:
Interaksie met die kannabinoïedtoets:
Efavirens bind nie aan die kannabinoïedreseptore nie. Vals-positiewe urientoetse is met die Kannabinoïedtoets resultate in nie-MIV besmette vrywilligers wat efavirens gebruik het waargeneem, wanneer die Microgenics Cedia DAU Multi-Level THS bepaling vir sifting gebruik is. Negatiewe resultate is verkry wanneer meer spesifieke bevestigende toetse met gaschromatografie/massaspektrometrie gebruik is.

Ander interaksies:
Efavirens:
Middelinteraksiestudies is met efavirens en ander medisyne wat waarskynlik saam met medisyne wat as ondersoeksende gebruik sou word vir farmakokinetiese interaksie, uitgevoer. Geen klinies beduidende interaksie is tussen efavirens en sidovudien, lamivudien, asitromisien, flukonasool, lorasepam of paroksetien waargeneem nie. Enkel dosisse famotidien of 'n aluminium en magnesium teensuurmiddel met simetikoon het geen effek op die blootstelling aan efavirens gehad nie.
Emtrisitabien en tenofovir disoproksielfumaraat:
Geen klinies betekenisvolle middelinteraksies is tussen emtrisitabien en tenofovir, indinavir, stavudien, tenofovir DF en sidovudien waargeneem nie. Netso is geen klinies betekenisvolle interaksies tussen Tenofovir DF en abasavir, adefovirdipifoksiel, efavirens, emtrisitabien, indinavir, lamivudien, lopinavir/ritonavir, metadoon, nelfinavir, orale voorbehoedmiddels, ribavirien en sakinavir/ritonavir in studies wat in gesonde vrywilligers uitgevoer is, waargeneem nie.
Na veelvuldige dosering aan MIV-negatiewe indiwidue wat chroniese metadoon onderhoudsterapie, orale voorbehoedmiddels of 'n enkel dosis ribavirin ontvang het, was die plato tenofovir farmakokinetika soortgelyk aan dié wat in vorige studies waargeneem is. Dit dui op 'n tekort aan betekenisvolle middelinteraksies tussen hierdie middels en tenofovir DF.

SWANGERSKAP EN LAKTASIE:
Die gebruik van **TRIOLAR TABLETS** gedurende swangerskap word teenaangedui aangesien teratogenisiteit met efavirens in swangerskap aangetoon is (sien **KONTRA-INDIKASIES**).
Skeidingskontrasepsie behoort altyd in kombinasie met ander metodes van kontrasepsie (bv. orale of hormonale kontrasepsie) gebruik te word.
Vroue wat kan swanger raak behoort swangerskapstoetsing te ondergaan vóór inisiëring van behandeling met **TRIOLAR TABLETS** (sien **KONTRA-INDIKASIES**).
Moeders wat borsvoed: MIV-positiewe moeders behoort nie hul babas te borsvoed nie. Weens die potensiaal vir MIV-oordraging en die potensiaal vir ernstige newe-effekte in sogende babas, **behoort moeders aangesê te word om nie hul babas te borsvoed as hulle TRIOLAR TABLETS neem nie**.

DOSIS EN GEBRUIKSAANWYSINGS:
Volwassenes:
Die aanbevole dosis **TRIOLAR TABLETS** is een tablet een keer per dag. **TRIOLAR TABLETS** behoort op 'n leë maag geneem te word aangesien voedsel die blootstelling aan efavirens kan laat toeneem en dit kan 'n toename in die frekwensie van newe-effekte veroorsaak. Om die verdraagsaamheid teen efavirens te verbeter, word dit aanbeveel dat **TRIOLAR TABLETS** met slapenstyd geneem word.
Kinders en adolessente:
Weens 'n tekort aan data oor die veiligheid en effektiwiteit word **TRIOLAR TABLETS** nie vir kinders jonger as 18 jaar oud aanbeveel nie (sien **KONTRA-INDIKASIES**).
Ingekorte nierfunksie:
TRIOLAR TABLETS word nie aanbeveel vir pasiënte met matig tot erg ingekorte nierfunksie (kreatinienopruiming < 50 mℓ/min) nie.
Waar staking van behandeling met een van die komponente van **TRIOLAR TABLETS** aangedui of waar 'n aanpassing van die dosis vereis word, is aparte preparate van efavirens, emtrisitabien en tenofovir beskikbaar. Verwys asseblief na die indiwiduele voubiljette van hierdie medisyne.

NEWE-EFFEKTE:
EFAVIRENS (600 mg):
Metaboliese en voedingsafwykings:
Frekwensie onbekend: Massatoename en massaverlies, herverspreiding/akkumulasie van liggaamsvet, hipercholesterolemie, hipertrigliseridemie.
Psigiatriese afwykings:
Minder dikwels: Beneweling, verwardheid, ingekorte konsentrasievermoë, slaaploosheid, angs, abnormale drome, depressie, abnormale denke, amnesie, delirium, emosionele onstabiliteit, euforie, hallusinering, psigose.
Frekwensie onbekend: Delusies, ontoepaslike gedrag, erge akute depressie (insluitende selfmoordidees en -pogings), neurose, vervolgingswaan, apatie, manie.
Afwykings van die senuweestelsel:
Dikwels: Duiseligheid, hoofpyn, slaapsug.
Minder dikwels: Abnormale koördinasie, ataksie, stuipaanvalle, migraine hoofpyne, neuralgie, parestesie, perifere neuropatie, spraakafwyking, bewerasie, hipoëstesie
Oogafwykings:
Minder dikwels: Abnormale visie.
Afwykings van die oor en labirint:
Minder dikwels: Tinnitus, vertigo.
Hartafwykings:
Minder dikwels: Hittegloede, hartkloppings tagikardie.
Respiratoriese, bors- en mediastinale afwykings:
Minder dikwels: Asma, boonste lugweginfeksies, sinusitis.
Frekwensie onbekend: Dispnee.
Gastroïntestinale afwykings:
Dikwels: Naarheid, braking, diarree.
Minder dikwels: Gastritis, gastroënteritis, gastro-esofagale refluks, toename in eetlus, smaakafwykings.
Frekwensie onbekend: Hardlywigheid, wanabsorpsie.
Hepatobileêre afwykings:
Minder dkwels: Hepatitis.
Frekwensie onbekend: Toename in lewerensieme, lewerversaking
Afwykings van die vel en subkutane weefsels:
Dikwels: Verspreide makulopapulêre uitslag.
Minder dikwels: Erge uitslag geassosieer met blaasvorming, vogtige velafskilfering of -ulserasie, aknee, alopesie, ekseem, follikulitis, seborree, velafskilfering, urtikarie.
Frekwensie onbekend: Hittegloede, erythema multiforme, naelafwykings, foto-allergiese dermatitis, velverkleuring, Stevens-Johnson se sindroom.
Muskuloskeletale, bindweefsel- en beenafwykings:
Minder dikwels: Artralgie, mialgie.
Frekwensie onbekend: miopatie.
Reproduksiestelsel- en borsafwykings:
Minder dikwels: Impotensie, afname in libido, toename in libido.
Frekwensie onbekend: Ginekomastie.
Afwykings van die immuunstelsel:
Frekwensie onbekend: Allergiese reaksie.
Algemene afwykings en kondisies by die plek van toediening:
Dikwels: Moegheid.
Minder dikwels: Astenie, malaise, pyn, sinkopee, griepagtige simptome, alkoholintoleransie, hittegloede.

EMTRISITABIEN (200 mg):
Afwykings van die senuweestelsel:
Dikwels: Hoofpyn.
Frekwensie onbekend: Astenie, duiseligheid, neuropatie, perifere neuritis, parestesie.
Psigiatriese afwykings:
Frekwensie onbekend: Slaapafwykings (abnormale drome, slaaploosheid), depressie afwyking.
Gastroïntestinale afwykings:
Dikwels: Naarheid, braking, diarree.
Frekwensie onbekend: Buikpyn, dispepsie.
Afwykings van die vel en subkutane weefsels:
Dikwels: Uitslagepisodes (insluitende uitslag, pruritus, makulopapulêre uitslag, urtikarie, vesikobulleuse uitslag, pustulêre uitslag en allergiese reaksie).
Frekwensie onbekend: Velverkleuring, gemanifesteer deur hiperpigmentasie op die handpalms en/of voetsole.
Muskuloskeletale en bindweefselafwykings:
Frekwensie onbekend: Artralgie, mialgie.
Afwykings van die bloed- en limfsisteem:
Frekwensie onbekend: Neutropenie, anemie.
Nier en urienafwykings:
Dikwels: Verhoging in kreatinienkinase.
Respiratoriese, bors- en mediastinale afwykings:
Frekwensie onbekend: Toename in hoes en rinitis.
Hepatobileêre afwykings:
Frekwensie onbekend: Verhoogde lewerensiem konsentrasie en hiper-bilirubinemie.
Metaboliese en voedingsafwykings:
Frekwensie onbekend: Melksuurasidose, gewoonlik geassosieer met erge hepatomegalie en steatose, hipertrigliseridemie, hiperglukemie.

TENOFOVIR (300 mg):
Dikwels: Naarheid, braking, diarree, buikpyn, winderigheid, dispepsie en anoreksie.
Minder dikwels: Verhoogde serumamilase konsentrasie, pankreatitis.
Frekwensie onbekend: Buikpyn, dispepsie.
Afwykings van die senuweestelsel:
Frekwensie onbekend: Hoofpyn, astenie, duiseligheid, perifere neuropatie (insluitende perifere neuritis, neuropatie).
Psigiatriese afwykings:
Frekwensie onbekend: Depressie, angs.
Afwykings van die vel en subkutane weefsels:
Frekwensie onbekend: Veluitslag (insluitende uitslag, pruritus, makulopapulêre uitslag, urtikarie, vesikulobulleuse uitslag, pustulêre uitslag).
Muskuloskeletale en bindweefselafwykings:
Frekwensie onbekend: Rugpyn, artralgie, mialgie.
Respiratoriese, bors- en mediastinale afwykings:
Frekwensie onbekend: Borspyn, pneumonie, dispnee.
Afwykings van die bloed- en limfsisteem:
Frekwensie onbekend: Neutropenie, hematurie.
Hepatobileêre afwykings:
Frekwensie onbekend: Verhoogde lewerensieme en hepatitis.
Metaboliese en voedingsafwykings:
Dikwels: Hiperfosfatemie.
Frekwensie onbekend: Melksuurasidose, gewoonlik geassosieer met erge hepatomegalie en steatose, hipertrigliseridemie, hiperglukemie.
Nier- en urienafwykings:
Frekwensie onbekend: Toename in kreatinienkinase vlakke, nefritis, nefrogeniese diabetes insipidus, ingekorte nierfunksie, akute nierversaking en effekte op die proksimale nierbuisies, insluitende Fanconi se sindroom, nierversaking, proksimale tubulopatie, proteïenurie, akute buisnekrose.
Afwykings van die immuunstelsel:
Frekwensie onbekend: Allergie, allergiese reaksies.
Algemene afwykings:
Frekwensie onbekend: Koors, sweet, massaverlies.

BEKENDE SIMPTOME VAN OORDOSERING EN BESONDERHEDE VAN DIE BEHANDELING DAARVAN:
In die geval van oordosering moet die pasiënt vir tekens van toksisiteit gemonitor word en waar nodig moet standaard ondersteunende behandeling toegedien word.
Efavirens:
Toename in senuweestelsel simptome en onwillekeurige spiersametrekkings is in pasiënte wat 600 mg twee keer per dag neem, aangemeld.
Die behandeling van oordosering met efavirens behoort uit algemene ondersteunende maatreëls te bestaan. Dit behoort monitering van lewenstekens en waarneming van die pasiënt se kliniese kondisie in te sluit. Geaktiveerde houtskool kan toegedien word om te help met die verwydering van ongeabsorbeerde medisyne. Dit is onwaarskynlik dat dialise enige beduidende hoeveelheid efavirens uit die bloed sal verwyder, aangesien die medisyne hoogs proteïengebonde is.
Emtrisitabien:
Behandeling met hemodialise verwyder ongeveer 30 % van die emtrisitabien dosis oor 'n 3-ure dialiseperiode wat binne 1,5 ure na die dosering met emtrisitabien begin (Bloedvloeitempo van 400 mℓ/min en 'n dialiseervloeitempo van 600 ml/min). Dit is nie bekend of emtrisitabien met peritoneale dialise verwyder kan word nie.
Tenofovir disoproksielfumaraat:
Tenofovir word effektief deur hemodialise verwyder met 'n ekstraksie koëffisiënt van ongeveer 54 %. Na 'n enkel 300 mg dosis tenofovir disoproksielfumaraat, verwyder 'n vier-ure dialise sessie ongeveer 10 % van die toegediende tenofovir dosis.

IDENTIFIKASIE:
Pienk, kapsulevormige, bikonvekse, filmbedekte tablette met "CL 81" op die een kant gedruk en skoon aan die ander kant.

AANBIEDING:
HDPE houer:
Tablette word in 'n wit, ondeursigtige, ronde 100 mℓ (28 tablette) of 120 mℓ (30 tablette) HDPE houer met 'n 38 mm nek, toegemaak met 'n 38 mm wit onderursigtige polipropileen geribde deksel met 'n induksie seëlprop. Elke houer bevat 28 of 30 tablette.

BERGINGSINSTRUKSIES:
Bewaar by of benede 25 °C. Beskerm teen lig.
Hou die HDPE houer dig gesluit.
HOU BUITE BEREIK VAN KINDERS.

REGISTRASIENOMMER:
47/20.2.8/1006

NAAM EN ADRES VAN DIE HOUER VAN DIE SERTIFIKAAT VAN REGISTRASIE:
Macleods Pharmaceuticals SA (Edms.) Bpk.
Kantoorblok 1
Bassonia Estate Office Park (Oos)
Cussoniarylaan 1
Bassonia Rock, Uitb. 12
Alberton.

DATUM VAN PUBLIKASIE VAN HIERDIE INLIGTINGSBROSJURE:
Die datum op die registrasiesertifkaat: 5 Junie 2014
Die datum van die mees onlangse hersiende voubiljet soos goedgekeur deur die Raad: 17 Februarie 2017

INLIGTINGSBLAD VIR PASIËNTE

SKEDULERINGSTATUS: S4

EIENDOMSNAAM, STERKTE EN FARMASEUTIESE VORM
TRIOLAR TABLETS (filmbedekte tablette)
Efavirens 600 mg, emtrisitabien 200 mg en tenofovir disoproksielfumaraat 300 mg.

Lees die hele brosjure sorgvuldig voordat u begin om **TRIOLAR TABLETS** te neem.
- Hou hierdie blaadjie. U mag dit moontlik weer wil lees.
- Indien u enige verdere vrae het, moet u asseblief u dokter of apteker raadpleeg. **TRIOLAR TABLETS** is vir u persoonlik voorgeskryf en u behoort nie u medisyne met ander mense te deel nie. Dit mag hulle skade aandoen, ookal het hulle dieselfde simptome as u.

WAT TRIOLAR TABLETS BEVAT
Elke filmbedekte tablet bevat 600 mg efavirens, 200 mg emtrisitabien en 300 mg tenofovir disoproksielfumaraat.
Ander bestanddele sluit mikrokristallyne sellulose, kroskarmellose natrium, hidroksipropielsellulose, natriumlourielsulfaat, magnesiumstearaat (plantaardig), gepregelatiniseerde stysel, polivinielalkohol, titaandioksied (C.I. 77891), poliëtileenglikol, talk, rooi ysteroksied (C.I. 77491) en swart ysteroksied (C.I. 77499) in. Suikervry.

WAARVOOR TRIOLAR TABLETS GEBRUIK WORD
TRIOLAR TABLETS word gebruik om Menslike Immuuntekortvirus (MIV) infeksie in volwassenes te behandel. **TRIOLAR TABLETS** word alleen of in kombinasie met ander anti-MIV medisyne gebruik om MIV-1 infeksie te behandel.

VOORDAT U TRIOLAR TABLETS NEEM
Moenie TRIOLAR TABLETS neem nie:
- As u hipersensitief (allergies) teen efavirens, emtrisitabien en tenofovir disoproksielfumaraat of enige van die ander bestanddele van **TRIOLAR TABLETS** is
- As u aan nierprobleme ly.
- As u swanger is of borsvoed.
- As u tans enige van die volgende medisyne gebruik:
  - astemisool (gebruik om hooikoors en ander allergieë te behandel)
  - kisapried (gebruik om sooibrand te behandel)
  - bepridiel (gebruik om hartsiekte te behandel)
  - ergotalkaloïede (bv. ergotamien, dihidroërgotamien, ergonovien en metielergonovien) (gebruik om migraine en troshoofpyne te behandel)
  - midasolam of triasolam (gebruik om u te help slaap)
  - pimosied (gebruik om sekere geestessiektes te behandel)
  - vorikonasool (vir swaminfeksies).

As u enige van die hierdie medisyne gebruik, moet u onmiddellik u dokter in kennis stel. Die neem van hierdie medisyne saam met **TRIOLAR TABLETS** kan ernstige of lewensbedreigende newe-effekte veroorsaak of kan veroorsaak dat hierdie medisyne nie werk nie.

Neem spesiale sorg met TRIOLAR TABLETS:

TRIOLAR TABLETS kan tot ernstige probleme met u lewer lei, of te veel suur in u bloed veroorsaak. Indien dit nie behandel word nie, kan dit tot die dood lei. U behoort vir etlike maande noukeurig deur u dokter gemonitor te word as u met HBV besmet is en besluit om met die gebruik van TRIOLAR TABLETS te staak.

- **TRIOLAR TABLETS** kan melksuurasidose veroorsaak, saam met 'n vergrootte lewer, wat fataal kan wees. Diep, vinnige asemhaling, lomerigheid en simptome soos naarheid, braking en maagpyn kan op die ontwikkeling van melksuurasidose dui. Melksuurasidose kom meer dikwels in vroue voor. Pasiënte wat oorgewig is het 'n groter risiko.
- Stel u dokter in kennis as u aan lewersiekte (insluitende hepatitis B) ly. Onafhanklik van 'n geskiedenis van lewersiekte, sal u dokter gereelde bloedtoetse oorweeg om te kyk hoe u lewer funksioneer.
- As u kind gedurende swangerskap aan **TRIOLAR TABLETS** blootgestel is, moet u hom/haar onmiddellik na u dokter te neem as hy/sy bleek lyk, swak is, die hele tyd lomerig is, vinniger asemhaal, vinnige hartklop het en die kind lyk asof hy/sy nie massa optel nie, braak, koors, seer keel of mondulkusse het, styf lyk of stuipaanvalle het of abnormale gedrag toon. U dokter sal bykomende mediese en laboratoriumtoetse op u kind doen.
- **TRIOLAR TABLETS** kan inflammasie van die pankreas veroorsaak. Stel u dokter in kennis erge boonste maagpyn met naarheid en braking ondervind.
- Stel u dokter in kennis as u enige lewersiekte insluitende hepatitis B of C gehad het, aangesien die behandeling met **TRIOLAR TABLETS** in pasiënte met lewersiekte moontlike ernstige newe-effekte wat die lewer aantas, insluitende die dood kan veroorsaak.
- U dokter sal u lewerfunksie moniteer deur gereelde bloedtoetse uit te voer.
- As u aan 'n aanhoudende hepatitis B infeksie ly, moet u nie sonder u dokter se advies met die gebruik van **TRIOLAR TABLETS** staak nie, aangesien die hepatitis kan terugkeer. Die hepatitis kan ook baie ernstiger wees as u aan 'n ernstige lewersiekte ly.
- Stel u dokter in kennis as u enige medisyne gebruik wat efavirens, emtrisitabien of tenofovirdisoproksiel, of lamivudien of adefovirdipivoksiel bevat. **TRIOLAR TABLETS** behoort nie met enige van hierdie medisyne geneem te word nie.
- Stel u dokter in kennis as u St. John se kruid (*Hypericum perforatum*) ('n kruiemiddel vir depressie en angs) gebruik. St. John se kruid en **TRIOLAR TABLETS** behoort nie saam geneem te word nie
- Stel u dokter in kennis as u aan 'n niersiekte ly of as toetse aangetoon het dat u aan nierprobleme ly. **TRIOLAR TABLETS** kan u niere aantas.
- **TRIOLAR TABLETS** word gewoonlik nie saam met ander middels wat u niere kan beskadig, geneem nie. As dit onafwendbaar is sal u dokter u nierfunksie moniteer.
- Veluitslag kan deur **TRIOLAR TABLETS** veroorsaak word. As u enige tekens van 'n erge uitslag met blasievorming en koors waarneem, moet u met die gebruik van **TRIOLAR TABLETS** ophou en onmiddellik u dokter raadpleeg.
- Stel u dokter in kennis as u 'n geskiedenis van geestessiektes insluitende depressie, of van middel- of alkoholmisbruik het. Stel u dokter onmiddellik in kennis as u depressief is, of selfmoord- of vreemde gedagtes het.
- Stel u dokter in kennis as u al ooit stuipaanvalle gehad het of medikasie vir stuipaanvalle neem.
- Sommige pasiënte wat kombinasie antiretrovirusterapie neem kan 'n beensiekte by name osteonekrose (afsterwing van beenweefsel weens 'n verlies aan bloedtoevoer na die been) ontwikkel. Tekens van osteonekrose is gewrigstyfheid en -pyn (veral in die heup, knie en skouer) en moeite met beweging. Stel u dokter in kennis as u enige van hierdie tekens waarneem.
- **TRIOLAR TABLETS** verminder die beenmineraaldigtheid wat tot frakture kan lei. U dokter mag kalsium en vitamien D supplemente voorskryf terwyl u **TRIOLAR TABLETS** neem.
- **TRIOLAR TABLETS** kan die vorm van u liggaam verander deur die vetverspreiding te verander. U mag vet van u bene, arms en gesig verloor en/of vet om die buikarea en interne organe versamel, groter borste of vetknoppe op die agterkant van die nek (buffelskof) ontwikkel.
- As u aan gevorderde MIV-siekte (VIGS) ly en enige infeksie het, kan u akute simptome van die infeksie of inflammasie en 'n agteruitgang van die simptome van 'n reeds bestaande infeksie ontwikkel wanneer behandeling met **TRIOLAR TABLETS** begin word. As u tekens van inflammasie of infeksie of 'n agteruitgang daarvan waarneem, moet u onmiddellik u dokter in kennis stel.
- U sal **TRIOLAR TABLETS** elke dag moet neem. **TRIOLAR TABLETS** help om u kondisie te beheer en vordering van die siekte te vertraag, maar dit is nie 'n genesing vir MIV nie. U mag aanhou om ander infeksies en siektes wat met MIV geassosieer word, op te doen. Bly in gereelde kontak met u dokter. Moenie met die medikasie stop voordat u nie u dokter geraadpleeg het nie.
- Die behandeling met **TRIOLAR TABLETS** verminder nie die risiko van oordraging van MIV na ander deur seksuele kontak of bloedoordraging (bv. bloedoortappings en deel van naalde) nie. U behoort toepaslike voorsorgmaatreëls te gebruik om dit te voorkom.
- Die veiligheid en effektiwiteit van **TRIOLAR TABLETS** in kinders en pasiënte jonger as 18 jaar oud vasgestel nie.
- **TRIOLAR TABLETS** word nie in bejaardes ouer as 65 aanbeveel nie.
- **TRIOLAR TABLETS** kan die bloedcholesterol-, trigliseried- en suikervlakke in u bloed verhoog en u dokter sal met gereelde tussenposes bloedtoetse uitvoer om u cholesterol-, trigliseried- en suikervlakke te monitor.

Die neem van TRIOLAR TABLETS saam met voedsel en vloeistof:
TRIOLAR TABLETS behoort sonder voedsel geneem te word. Alkohol behoort vermy te word.

SWANGERSKAP EN BORSVOEDING
Swangerskap :
- U behoort nie swanger te raak as u **TRIOLAR TABLETS** neem nie. Misvormings is in fetusse van diere wat met **TRIOLAR TABLETS** gedurende dragtigheid behandel is, waargeneem.
- Stel u dokter onmiddellik in kennis as u swanger is of beoog om swanger te raak.
- As u 'n vrou is wat **TRIOLAR TABLETS** neem, behoort 'n betroubare vorm van skeidingskontrasepsie (bv. kondoom) altyd gebruik te word saam met ander metodes van voorbehoeding, insluitende orale (die pil) of ander hormonale voorbehoedmiddels (bv. implante, inspuitings) gebruik te word.
- Moenie **TRIOLAR TABLETS** neem as u swanger is nie.

Borsvoeding:
- Moenie borsvoed as u **TRIOLAR TABLETS** neem nie aangesien dit ernstige skade aan u baba kan verrig. As u aan MIV ly behoort u nie onder enige omstandighede u baba te borsvoed nie aangesien u die MIV na u baba kan oordra.

As u swanger is of u baba borsvoed, moet u asseblief u dokter, apteker of ander gesondheidsbeampte vir advies nader.

Bestuur en die gebruik van masjinerie:
TRIOLAR TABLETS kan duiseligheid, ingekorte konsentrasievermoë en/of lomerigheid veroorsaak. As u duiselig of lomerig voel terwyl u **TRIOLAR TABLETS** neem moet u nie bestuur of met enige gereedskap of masjinerie werk nie.

Die neem van ander medisyne saam met TRIOLAR TABLETS:

Stel altyd u professionele gesondheidswerker in kennis as u enige ander medisyne neem. Dit sluit komplementêre en tradisionele medisyne in.

- Stel u dokter in kennis as u enige ander medisyne gebruik of onlangs gebruik het.
- Stel u dokter in kennis as u efavirens, abasavir, emtrisitabien, tenofovir, indinavir of lamivudien (vir MIV-infeksie) neem.
- As u tans enige van die volgende medisyne neem:
  - Kisapried (gebruik om sooibrand te behandel)
  - Bepridiel (gebruik om hartsiekte te behandel)
  - Ergotalkaloïede (bv. ergotamien, dihidroërgotamien, ergonovien en metielergonovien) (gebruik om migraine en troshoofpyne te behandel)
  - Midasolam of triasolam (gebruik om u te help slaap)
  - Pimosied (gebruik om sekere geestessiektes te behandel)
  - Vorikonasool (vir swaminfeksies).

As u enige van hierdie medisyne neem, moet u onmiddellik u dokter daarvan in kennis stel.
- Stel u dokter in kennis as u atasanavir en/of lopinavir/ritonavir (vir MIV-infeksie) nee. As u enige van hierdie medisyne neem, mag dit nodig wees dat u dokter u terapie meer deeglik moet monitor of u mag moontlik nie **TRIOLAR TABLETS** kan gebruik nie.
- Stel u dokter in kennis as u enige medisyne neem wat didanosien (vir MIV-infeksie) neem. Die neem van **TRIOLAR TABLETS** saam met ander antivirusmiddels wat didanosien bevat, kan die didanosienvlakke in u bloed verhoog. Inflammasie van die pankreas en neuropatie (senuweeafwykings) kan voorkom. U dokter sal dit noukeurig oorweeg om u met kombinasies van tenofovir en didanosien te behandel.
- Medisyne wat gebruik word om bloedvette te verminder (statiene): Atorvastatien, pravastatien, simvastatien. **TRIOLAR TABLETS** kan die hoeveelheid statiene in u bloed verminder. U dokter sal u cholesterolvlakke nagaan en dit oorweeg om die dosis van u statien te verander, indien nodig.
- Medisyne wat gebruik word om stuipaanvalle te behandel (antistuipmiddels): Karbamasepien, fenitoïen, fenobarbital. **TRIOLAR TABLETS** kan die hoeveelheid antistuipmiddel in u bloed verminder. Karbamasepien kan die hoeveelheid efavirens, een van die komponente van **TRIOLAR TABLETS**, in u bloed verminder. U dokter mag dit oorweeg om 'n ander antistuipmiddel aan u te gee.
- Medisyne wat gebruik word om bakteriese infeksies te behandel: Klaritromisien, rifabutien, rifampisien. U dokter mag dit oorweeg om die dosis te verander of 'n ander antibiotika aan u te gee Boonop kan u dokter besluit om 'n ekstra dosis efavirens te gee om u MIV-infeksie te behandel.
- Medisyne wat gebruik word om swaminfeksies te behandel (swamweerders). Itrakonasool of ketokonasool. **TRIOLAR TABLETS** kan die hoeveelheid itrakonasool of ketokonasool in u bloed verminder.
- Hormonale kontrasepsie soos die pil, 'n inspuitbare voorbehoed-middel (bv. Depot-Provera). U moet altyd 'n betroubare metode van skeidingskontrasepsie soos 'n kondoom gebruik aangesien **TRIOLAR TABLETS** hormonale voorbehoedmiddels minder effektief kan maak.
- Metadoon, 'n middel om afhanklikheid te behandel, aangesien u dokter u metadoon dosis moet verander.
- Sertralien, 'n middel wat gebruik word depressie te behandel, aangesien u dokter moontlik u sertralien dosis moet verander.
- Diltiasem of soortgelyke medisyne (kalsiumkanaalblokkeerders). Wanneer u begin om **TRIOLAR TABLETS** te neem, mag u dokter die dosis van die kalsiumkanaalblokkeerder aanpas.
- Warfarien (medisyne wat gebruik word om bloedklonting te verminder). Dit mag vir u dokter nodig wees om die warfarien dosis aan te pas.
- St. John se kruid (*Hypericum perforatum*) ('n kruimiddel wat vir depressie en angs gebruik word) word nie saam met **TRIOLAR TABLETS** aanbeveel nie.
- Stel u dokter in kennis as u enige ander medisyne gebruik wat u nierfunksie mag inkort. Sommige voorbeelde sluit die volgende in:
  - Aminoglikosiede (vir bakteriese infeksies)
  - Adefovirdipivoksiel (vir virusinfeksies)
  - Sidofovir (vir virusinfeksies)
  - Asiklovir (vir virusinfeksies)
  - Valasiklovir (vir virusinfeksies)
  - Gansiklovir (vir virusinfeksies)
  - Valgansiklovir (vir virusinfeksies)
  - Amfoterisien B (vir swaminfeksies)
  - Foskarnet (vir virusinfeksies)
  - Pentamidien (vir infeksies)
  - Interleukin-2 (vir die behandeling van kanker).

HOE OM TRIOLAR TABLETS TE NEEM

Neem TRIOLAR TABLETS altyd presies soos deur u dokter voorgeskryf. Bevestig met u dokter of apteker as u onseker is. As u van mening is dat die effek van TRIOLAR TABLETS te sterk of te swak is, moet u u dokter of apteker raadpleeg.

- Bly onder u gesondheidswerker se sorg wanneer u **TRIOLAR TABLETS** neem. Moenie u behandeling verander of staak sonder om eers met u gesondheidswerker te praat nie.
- Die normale dosis van **TRIOLAR TABLETS** is een tablet, met water, een keer per dag met slapenstyd, sonder voedsel.

As u te veel TRIOLAR TABLETS geneem het:
- Kry nood mediese hulp as u dink dat u te veel **TRIOLAR TABLETS** geneem het.

In die geval van oordosering, raadpleeg u dokter of apteker. As hulle nie beskikbaar is nie, kontak u naaste hospitaal of gifbeheersentrum.

As u vergeet het om TRIOLAR TABLETS te neem:
As u vergeet het om 'n dosis te neem, neem dit so gou as wat u daarvan onthou en gaan dan voort soos gewoonlik. Moenie 'n dubbel dosis neem om vir 'n oorgeslaande indiwiduele dosis op te maak nie.

MOONTLIKE NEWE-EFFEKTE
TRIOLAR TABLETS kan newe-effekte hê.
Nie al die newe-effekte wat vir hierdie medisyne aangemeld is, word in hierdie brosjure ingesluit nie. As u algemene gesondheid agteruitgaan of as u enige ongewone effekte ondervind terwyl u **TRIOLAR TABLETS** neem, moet u asseblief u dokter, apteker of ander professionele gesondheidswerker om advies raadpleeg.

Kry nood mediese hulp as u enige een van hierdie **tekens van 'n allergiese reaksie waarneem:**
- Urtikarie, moeite met asemhaling, swelling van u gesig, lippe, tong of keel.

Raadpleeg onmiddellik u dokter as u enige van die volgende newe-effekte waarneem:
- Melksuurasidose (erge toename van melksuur in u bloed, 'n ernstige newe-effek wat fataal kan wees) - Die volgende newe-effekte kan tekens van melksuurasidose wees: diep, vinnige asemhaling, lomerigheid, naarheid, braking en maagpyn.
- Lewerbeskadiging - naarheid, maagpyn, lae koors, verlies aan eetlus, donkergekleurde urien, kleigekleurde stoelgang, geelsug, (geel verkleuring van die vel of oë).
- Rugpyn veroorsaak deur nierprobleme, insluitende nierversaking. U dokter mag bloedtoetse doen om vas te stel of u niere behoorlik funksioneer.
- Koors, kouekoors, seer keel, hoes of ander tekens van infeksie.
- Psigiatriese simptome insluitende verwardheid, erge depressie, selfmoordidees, aggressie, uitermatige vrees, hallusinasies of ongewone gedrag.
- Koors met erge blaasvorming, afskilfering en rooi veluitslag of enige erge velreaksie.
- Stuipaanvalle.

Stel u dokter in kennis as u enige van die volgende newe-effekte waarneem of as hierdie simptome kwellend is of nie wil verdwyn nie:
Dikwels voorkomende newe-effekte:
- Moegheid
- Duiseligheid, lomerigheid
- Hoofpyn
- Naarheid, braking, diarree, maagpyn, indigestie, omgekrapte maag

Minder dikwels voorkomende newe-effekte:
- Gevoelloosheid, prikkeling, spelde en naalde, bewerasie
- Moeite met konsentrasie, vergeetagtigheid, verwardheid
- Moeite om aan die slaap te raak, abnormale drome
- Afwykings van koördinasie en balans
- Abnormale euforiese gevoel
- Gevoel van depressie of angs
- Onduidelike visie
- Suising in die ore en 'n draaigevoel (vertigo)
- Sinusitis
- Hartkloppings (vinnige ongereelde aksie van die hart), toename in die harttempo
- Asthma
- Toename of afname in eetlus
- Smaakafwykings
- Inflammasie van die pankreas (erge buikpyn)
- Veluitslag, jeuk, toename is sweet, ekseem, haarverlies aknee, veranderinge in vel- en naelkleur.
- Spier- of gewrigspyn
- Impotensie (verlies aan manlike seksuele funksionering) toename en afname in seksdrang (libido)
- Tekort aan energie (algemene gevoel van ongesteldheid
- Hittegloede

Frekwensie onbekend:
- Griepagtige simptome, hoes, loperige of verstopte neus
- Pyn, rugpyn, borspyn
- Kortademheid
- Hardlywigheid
- Borsvergroting in mans
- Bloed in die urien, inflammasie van die niere, dikwelse urinering en dorstigheid
- Massatoename of massaverlies, verandering in die vorm van en plek van liggaamsvet (veral in u arms, bene, gesig, nek, borste en middel)

Bloedtoetse kan ook die volgende aandui:
- Afname van fosfaatvlakke in die bloed
- Toename in die vlakke van kreatienkinase in die bloed wat tot spierpyn en -swakheid kan lei.
- Anemie (lae rooibloedseltelling)
- Lae witbloedseltelling ('nlaer witbloedseltelling kan veroorsaak dat u meer tot infeksies neig)
- Toename in vetsuur- (trigliseriede), bilirubien- of suikervlakke in die bloed
- Probleme met die lewer of pankreas
- Afname in kalium in die bloed
- Toename in kreatinien in die bloed
- Proteïene in die urien

As u enige newe-effekte ondervind wat nie in hierdie blaadjie genoem word nie, moet u asseblief u dokter raadpleeg.

OPBERGING EN WEGDOEN VAN TRIOLAR TABLETS
Bewaar by of benede 25 °C (kamertemperatuur). Beskerm teen lig.
Hou die HDPE houer dig gesluit.
BERG ALLE MEDISYNE BUITE BEREIK VAN KINDERS.

Neem alle ongebruikte medisyne na u apteker terug.
Moenie enige ongebruikte medisyne in die drein of riolering (bv. toilette) weggooi nie.

AANBIEDING:
TRIOLAR TABLETS
HDPE houer:
Tablette word in 'n wit, ondeursigtige, ronde 100 mℓ (28 tablette) of 120 mℓ (30 tablette) HDPE houer met 'n 38 mm nek, toegemaak met 'n 38 mm wit onderursigtige polipropileen geribde deksel met 'n induksie seëlprop. Elke houer bevat 28 of 30 tablette.

IDENTIFIKASIE:
TRIOLAR TABLETS
Pienk, kapsulevormige, bikonvekse, filmbedekte tablette met "CL 81" op die een kant gedruk en skoon aan die ander kant.

REGISTRASIENOMMER - VERWYSINGSNOMMER
47/20.2.8/1006

NAAM EN ADRES VAN DIE REGISTRASIEHOUER
Macleods Pharmaceuticals SA (Edms.) Bpk.
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PACKAGING RESEARCH & DEVELOPMENT

Restricted Circulation

(Front Page)

ARTWORK / PRINTPROOF APPROVAL FORM

1. Product: TRIOLAR TABLETS	
2. Country: South Africa	**3. Packaging component: Package Insert & Patient Information Leaflet**
4. No. of Colours: 1 Colour	**5. Pantone Shade No.: Black**
6. Specification: 40 gsm bible paper	
7. Machine Layout No.: NA	**8. Dimensions: 735 x 490 mm**
9. Design / Style: NA	**10. Item code No.: PM03311101**
11. Artwork has been made: Actual Size	**12. Pharma code No.: 26274 mini**
13. Barcode/NDC no: NA	**14. Supersedes Item code No: NA**
15. Revision no: 00	**16. File Name : E:\ANDA Regulatory\South Africa\Efa, Emi, Teno\Activo-Triolar\04\TRIOLAR PI & PIL common PM03311101.cdr**
Approved By:	**17. Location: Daman / Baddi**

PRD	M.A. HOLDER	MEDICAL/RAD	QC	PRODN	QA
	Rashmi Gosai Digitally signed by Rashmi Gosai DN: cn=Rashmi Gosai, o=Macleods SA, ou=Macleods SA, email=rgosai@macleodspharma.com, c=ZA Date: 2020.05.25 12:19:11 +02'00'				

Note: 1. To follow overleaf checklist for approval of Artwork / Print proof.

Instructions to Vendor :

1. Before processing, please ensure First pull out / Commercial supply should match with approved Artwork with respect to Design, Size, Fonts & Text.
2. Print proof to represent full printing area with Station Numbers.

FRM/CQA/021/04-01

Reason for revision :	Item code	Artwork Release Date	Artwork Implementation Date
1) New Artwork for South Africa	PM03311101		