TRIOLAR TABLETS
PM01876403

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**).
> **TRIOLAR TABLETS** IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION AND THE SAFETY AND EFFICACY OF **TRIOLAR TABLETS** HAVE NOT BEEN ESTABLISHED IN PATIENTS COINFECTED WITH HBV AND HIV-1. 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**).

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

PHARMACOLOGICAL ACTION:
Pharmacodynamics:
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.

Pharmacokinetics:
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 **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, Renal impairment**).

Patients with Hepatic Impairment
Efavirenz: The pharmacokinetics of efavirenz have not been adequately studied in patients with hepatic impairment (see **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 **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:
Lactic acidosis / Severe hepatomegaly with steatosis:
Lactic acidosis and severe hepatomegaly with steatosis including fatal cases, have been reported with the use of nucleoside analogues, alone or in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogues to any patient with known risk factors for liver disease, however, cases have also been reported in patients with no known risk factors. Treatment with **TRIOLAR TABLETS** should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).
Patients with HIV and hepatitis B virus co-infection:
It is recommended that all patients with HIV be tested for the presence of hepatitis B virus (HBV) prior to the initiation of therapy with antiretroviral agents. **TRIOLAR TABLETS** is not indicated for the treatment of chronic HBV infection and the safety and efficacy of **TRIOLAR TABLETS** have not been confirmed in patients with HBV and HIV co-infection. Severe acute exacerbations of hepatitis B have occurred in patients following the discontinuation of emtricitabine and tenofovir disoproxil fumarate. Patients with HBV and HIV co-infection who discontinue **TRIOLAR TABLETS** require close monitoring of their hepatic function for at least several months; this should include both clinical and laboratory follow-up. Appropriate initiation of anti-hepatitis B therapy may be necessary.
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 AND SPECIAL PRECAUTIONS**).
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-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.

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.
Antihistamine: astemizole	CONTRA-INDICATED due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.
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 agent: 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 regimes 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 safety and efficacy have not been established (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. It is not known whether efavirenz, emtricitabine or tenofovir are excreted in human milk. Due to the potential for HIV transmission and the potential for serious adverse reactions in breastfed infants, **mothers should be instructed not to breastfeed if they are taking 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 of 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 AND SPECIAL PRECAUTIONS:
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.

Special Precautions:
Lactic acidosis / Severe hepatomegaly with steatosis:
Routine testing of serum lactate levels in asymptomatic patients on ART is not recommended. Management of serum lactate levels is recommended only for patients presenting with clinical signs or symptoms consistent with lactic acidosis.
Lactate 2 to 5 mmol/l: monitor regularly and be alert for clinical signs.
Lactate 5 to 10 mmol/l without symptoms: monitor closely.
Lactate 5 to 10 mmol/l with symptoms: STOP all therapy. Exclude other causes (e.g. sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis, lymphoma).
Lactate greater than or equal to 10 mmol/l: STOP all therapy (80 % mortality in case studies).
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.
Nervous system and psychiatric symptoms:
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.
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.
Liver enzymes:
Monitoring of liver enzyme levels is recommended in patients with known or suspected history of hepatitis B or C infection and in patients treated with other medicines associated with hepatic toxicity. The benefit of continued therapy with **TRIOLAR TABLETS** has to be weighed against the unknown risks of significant hepatic toxicity in patients who show persistent elevations of serum transaminases to greater than 5 times the upper limit of the normal range (see **Side-Effects**).
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.
Fat Redistribution
Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.
Immune Reconstitution Syndrome
Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including **TRIOLAR TABLETS**. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii (carini)* pneumonia (PCP), or tuberculosis), which may necessitate further evaluation and treatment.
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.

Opportunistic infections:
Patients taking **TRIOLAR TABLETS** or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection. They should therefore remain under close clinical observation by medical practitioners with experience in the treatment of patients with HIV associated disease.
Transmission of HIV:
Patients must be advised that there is no proof that antiretroviral therapies, including **TRIOLAR TABLETS**, prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Patients must continue to use appropriate precautions.
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.

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:
Patients accidentally taking 600 mg twice daily have reported increased nervous system symptoms and involuntary muscle contractions. Treatment of efavirenz overdose should consist of general supportive measures. These should include vital sign monitoring and observation of the patient's clinical status. Activated charcoal may be administered to aid removal of unabsorbed medicine. Dialysis is unlikely to significantly remove 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 120 ml 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 from light.
Keep the HDPE containers 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
Stand 6 D & E, Growthpoint Business Park,
Halfway House,
Midrand
South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT:
5 June 2014.

TRIOLAR TABLETS

PATIENT INFORMATION LEAFLET

> 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.

S4

TRIOLAR TABLETS (Film-coated tablets)
Efavirenz, emtricitabine and tenofovir disoproxil fumarate

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

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. The safety and efficacy of TRIOLAR TABLETS in patients who are infected with both human immunodeficiency virus (HIV) and hepatitis B virus (HBV) have not been established. TRIOLAR TABLETS should not be used for treatment of chronic HBV infection. 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). **TRIOLAR TABLETS** should not be used to treat chronic hepatitis B virus infection (HBV; an on-going liver infection). Independent of a history of liver disease, your doctor will consider regular blood tests to check how your liver is working.
- 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.
- **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** has not been shown to 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:
- Do not take **TRIOLAR TABLETS** if you are pregnant. Malformations have been seen in foetuses from animals treated with **TRIOLAR TABLETS** during pregnancy; therefore, pregnancy should be avoided in women receiving **TRIOLAR TABLETS**.
- 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 breastfeed if you are taking **TRIOLAR TABLETS.**

> If you are pregnant or breastfeeding your baby while taking **TRIOLAR TABLETS**, please consult your doctor, pharmacist or other health care professional for advice.

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:

> **If you are taking other medicines on a regular basis, including complementary or traditional medicines, the use of TRIOLAR TABLETS with these medicines may cause undesirable interactions. Please consult your doctor, pharmacist or other healthcare professional, for advice.**

- 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:
  - 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.

- 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, talk to 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, seek help at the nearest hospital or poison control centre.

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 doses.

POSSIBLE SIDE-EFFECTS
TRIOLAR TABLETS can have side-effects.
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:
- weight gain or weight loss
- dizziness
- numbness, tingling, pins and needles
- tremor (shake)
- difficulty concentrating
- drowsiness
- difficulty falling asleep
- unusual dreams
- headache
- disturbances of co-ordination and balance
- forgetfulness
- confusion
- 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
- nausea, vomiting
- diarrhoea or constipation
- stomach pain
- indigestion
- upset stomach
- 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)
- fatigue or lack of energy
- hot flushes
- flu-like symptoms
- generally feeling unwell
- pain, back pain, chest pain
- shortness of breath
- cough
- runny or stuffy nose
- enlarged breasts in males
- blood in the urine, inflammation of the kidney, passing a lot of urine and feeling thirsty
- 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

> **Not all side-effects reported for TRIOLAR TABLETS are included in this leaflet. Should your general health worsen while taking TRIOLAR TABLETS please consult your doctor, pharmacist or other health care professional for advice.**

STORING AND DISPOSING OF TRIOLAR TABLETS
Store at or below 25 °C (room temperature). Protect from light. Keep the HDPE containers closed.
KEEP ALL MEDICINES OUT OF REACH AND SIGHT 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 120 ml 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
Stand 6 D & E, Growthpoint Business Park, Halfway House,
Midrand
South Africa

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SKEDULERINGSTATUS:

S4

EIENDOMSNAAM EN DOSEERVORM:
TRIOLAR TABLETTE (Filmbedekte tablette).

SAMESTELLING:
Elke filmbedekte tablet bevat 600 mg efavirens, 200 mg emtrisitabien en 300 mg tenofovirdisoproksielfumaraat. Suikervry.
Ander bestanddele sluit die volgende in: mikrokristallyne sellulose, kroskarmellose natrium, hidroksipropielsellulose, natriumlourielsulfaat, magnesiumstearaat (plantaardig), gegelatiniseerde stysel, polivinielalkohol, titaandioksied (C.I. Nr. 77891), poliëtileenglikol, talkum, rooi ysteroksied (C.I. Nr. 77941), swart ysteroksied (C.I. Nr. 77499).

> **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**).
> **TRIOLAR TABLETTE** WORD NIE VIR DIE BEHANDELING VAN CHRONIESE HEPATITIS B INFEKSIE (HBV) AANGEDUI NIE EN DIE VEILIGHEID EN EFFEKTIWITEIT VAN **TRIOLAR TABLETTE** IS NIE IN PASIËNTE WAT MET BEIDE HBV EN MIV-1 BESMET IS, VASGESTEL NIE. ERGE AKUTE VERERGERINGS VAN HEPATITIS B IS IN PASIËNTE WAT MET DIE GEBRUIK VAN EMTRISITABIEN OF TENOFOVIR, WAT KOMPONENTE VAN **TRIOLAR TABLETTE** IS, OPGEHOU HET, AANGEMELD. LEWERFUNKSIE BEHOORT NOULETTEND GEMONITOR TE WORD, MET BEIDE KLINIESE EN LABORATORIUMOPVOLG VIR TEN MINSTE ETLIKE MAANDE IN PASIËNTE WAT DIE GEBRUIK VAN **TRIOLAR TABLETTE** STAAK EN WAT MET BEIDE MIV EN HBV BESMET IS. WAAR VAN TOEPASSING MAG DIE INISIËRING VAN ANTIHEPATITIS B TERAPIE MOONTLIK GEREGVERDIG WORD (SIEN **WAARSKUWINGS**)

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

FARMAKOLOGIESE WERKING:
Farmakodinamika:
TRIOLAR TABLETTE is 'n vastedosis kombinasietablet wat efavirens, emtrisitabien en tenofovirdisoproksielfumaraat (tenofovir DF) bevat. Efavirens is 'n nie-nukleosied trutranskriptaseïnhibeerder; emtrisitabien is 'n sintetiese nukleosiedanaloog van sitidien en tenofovirdisoproksielfumaraat 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 TT en menslike 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-polimerase α, β, ε en mitochondriale DNA-polimerase γ.

Tenofovirdisoproksielfumaraat:
Tenofovir DF, 'n NTTI, is 'n asikliese nukleosiedfosfonaat diësteranaloog van adenosien monofosfaat en benodig aanvanklike diësterhidrolise vir omskakeling na tenofovir en daaropvolgende fosforilerings deur sellulêre ensieme om tenofovirdifosfonaat te vorm. Tenofovirdifosfonaat inhibeer die aktiwiteit van MIV-1 TT deur met die natuurlike substraat deoksiadenosien-5'-trifosfaat te kompeteer. Na inkorporering in die DNA, word die DNA-ketting getermineer. Tenofovirdifosfaat is 'n swak inhibeerder van soogdier DNA-polimerase α, β, en mitochondriale DNA-polimerase γ .

Antivirusaktiwiteit
Efavirenz, emtricitabine and tenofovirdisoproksielfumaraat:
In kombinasiestudies wat die *in vitro* antivirusaktiwiteit van emtrisitabien en efavirens saam, efavirens en tenofovir saam en emtrisitabien en tenofovirdisoproksielfumaraat saam geëvalueer het, is additiewe tot sinergistiese antiviruseffekte waargeneem.

Weerstand:
Efavirenz, emtricitabine and tenofovirdisoproksielfumaraat:
MIV-1 isolate wat 'n afname in vatbaarheid vir die emtrisitabien en tenofovirkombinasie getoon het, is *in vivo* geselekteer.
Na genotipiese ontleding is die M184V/I en/of K65R aminosuurvervangings in die virus TT geïdentifiseer.

Efavirens:
Kliniese isolate met laer *in vitro* vatbaarheid vir efavirens is verkry. Die mees dikwels waargenome aminosuurvervanging in kliniese studies met efavirens is K103N (54 %). Een of meer TT-vervangings by aminosuurposisies 98,100, 101, 103, 106, 108, 188, 190, 225, 227 en 230 is in pasiënte wat onsuksesvol met efavirens in kombinasie met ander antiretrovirusmiddels behandel is, waargeneem. Ander weerstandbiedende mutasies wat dikwels ontwikkel het, het L1001 (7 %), K101E/Q/R (14 %), V1081 (11 %), G190S/T/A (7 %), P225H (18 %) en M230I/L (11 %) ingesluit.
MIV-1 isolate met 'n verminderde vatbaarheid vir efavirens ('n meer as 380-voudige toename in EK_{90}-waarde) het vinnig met *in vitro* seleksie ontwikkel. Genotipiese karakterisering van hierdie virusse het mutasies geïdentifiseer wat tot enkel aminosuurvervangings L1001 of V179D, dubbelvervangings L1001/V1081, en driedubbel vervangings L1001I/V179D/ Y181C in TT gelei het.

Emtrisitabien:
MIV-isolate weerstandbiedend teen emtrisitabien is *in vitro* geselekteer. Die genotipiese ontleding van hierdie isolate het aangetoon dat 'n afname in die vatbaarheid vir emtrisitabien met 'n mutasie in die MIV TT-geen by kodon 184 geassosieer is. Hierdie mutasie het 'n aminosuurvervanging van metionien by valien of isoleusien (M184V/I) veroorsaak.

Tenofovirdisoproksielfumaraat:
Isolate van MIV-1 wat verminderde vatbaarheid vir tenofovir getoon het, is *in vitro* geselekteer. Hierdie virusse het 'n K65R mutasie in trutranskriptase uitgedruk en 'n 2- tot 4-voudige vermindering in vatbaarheid vir tenofovir getoon.

Kruisweerstand:
Efavirenz, emtricitabine and tenofovirdisoproksielfumaraat:
Kruisweerstand word onder NNTTIs herken. Dit is ook bekend dat kruisweerstand onder sekere NTTIs mag ontwikkel. Die M184V/I en/of K65R vervangings wat *in vitro* deur die kombinasie van emtrisitabien en tenofovir geselekteer is, word ook in sommige MIV-1 stamme uit indiwidue in wie behandeling met tenofovir in kombinasie met lamivudien of emtrisitabien en abasavir of didanosien misluk het, waargeneem. Kruisweerstand tussen hierdie middels kan daarom in pasiënte wie se virus een of beide van hierdie aminosuurvervangings huisves, ontwikkel.

Farmakokinetika:
Efavirens:
Absorpsie:
Piek efavirens plasmakonsentrasies van 1,6 – 9,1 M word 5 ure na enkel orale dosisse van 100 mg tot 1600 mg aan onbesmette vrywilligers bereik. Alhoewel dosisverwante toenames in K_{maks} en AOK vir dosisse van tot soveel as 1600 mg waargeneem word, is hierdie toenames minder as proporsioneel. Dit dui op 'n afname in absorpsie teen hoër dosisse. Plato plasmakonsentrasies word na 6 tot 10 dae bereik.
Verspreiding:
Efavirens word sterk aan plasmaproteïene gebind (ongeveer 99,5 – 99,75 %), hoofsaaklik aan albumien. Konsentrasies in serebrospinale vloeistof het gewissel van 0,26 tot 1,19 % (gemiddeld 0,69%) van die ooreenstemmende plasmakonsentrasies in MIV-1 besmette indiwidue wat 200 tot 600 mg efavirens een keer per dag vir ten minste een maand ontvang het. Dit is ongeveer drie keer meer as die nie-proteïengebonde (vrye) 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 onaktief teen MIV-1. CYP3A4 en CYP2B6 is die belangrikste isoënsiem betrokke by die metabolisme van efavirens. Deur induksie van die P450 ensiem induseer efavirens sy eie metabolisme.
Opruiming:
Efavirens besit 'n lang terminale halfleeftyd van 52 – 76 ure en 40 – 55 ure na enkel en veelvuldige dosisse, respektiewelik. Na die toediening van 'n radiogemerkte dosis, word 14 – 34 % van efavirens in die urien herwin (hoofsaaklik as metaboliete), terwyl 16 – 61 % in die feses herwin word (hoofsaaklik as die moedermiddel).

Emtrisitabien:
Die farmakokinetiese eienskappe van emtrisitabien word in Tabel 1 opgesom.
Absorpsie:
Na orale toediening van emtrisitabien (200 mg), word dit vinnig geabsorbeer, met piek plasmakonsentrasies wat na 1 – 2 ure na dosering voorkom.
Verspreiding:
Die *in vitro* binding van emtrisitabien aan menslike plasmaproteïene is <4 % en is onafhanklik van die konsentrasie oor die reikwydte van 0,02 – 200 g/ml.
Metabolisme en opruiming:
Na die toediening van radiogemerkte emtrisitabien word ongeveer 86 % in die urien en 13 % as metaboliete herwin. Die metaboliete van emtrisitabien sluit 3'-sulfoksieddiastereomere en hul glukuronsuurderivate in. Emtrisitabien word deur 'n kombinasie van glomerulêre filtrasie en aktiewe buissekresie opgeruim. Na 'n enkel dosis emtrisitabien (200 mg) is die plasmahalfleeftyd ongeveer 10 ure.

Tenofovirdisoproksielfumaraat:
Die farmakokinetiese eienskappe van tenofovirdisoproksielfumaraat word in Tabel 1 opgesom.
Absorpsie:
Na die orale toediening van tenofovir, word die maksimum serumkonsentrasies van tenofovir na 1,0 ± 0,4 uur bereik.
Verspreiding:
Die *in vitro* binding van tenofovir aan menslike plasmaproteïene is <0,7 % en is onafhanklik van konsentrasie oor die reikwydte 0,01 – 25 g/ml.
Metabolisme en opruiming:
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 uitgeskei. Na 'n enkel orale dosis van 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 (GV – 45,0)
Plasmaterminale opruimings-halfleeftyd[2] (uur)	10 (7,4 – 18,0	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
Suiwering/F[3] ml/min)	302 ± 94	1043 ±115
$Suiwering_{nier}$ (ml/min)	213 ± 89	243 ± 33

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

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

Spesiale populasies:
Pediatriese en bejaarde pasiënte
Farmakokinetiese studies met tenofovir DF is nie in pediatriese pasiënte (jonger as 18 jaar) 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 TABLETTE** word nie vir pediatriese toediening aanbeveel nie. Die farmakokinetika van efavirens, emtrisitabien en tenofovir is nie ten volle in bejaardes (ouer as 65 jaar) geëvalueer nie (sien **SPESIALE VOORSORGSMAATREËLS**)

Pasiënte met ingekorte nierfunksie
Efavirens:
Die farmakokinetika van efavirens is nie in pasiënte met ingekorte nierfunksie bestudeer nie; minder as 1 % word egter onveranderd deur die niere uitgeskei. Die impak van ingekorte nierfunksie op die opruiming van efavirens behoort derhalwe minimaal te wees.

Emtrisitabien en tenofovirdisoproksielfumaraat:
Die farmakokinetika van emtrisitabien en tenofovir DF verander in pasiënte met ingekorte nierfunksie. In pasiënte met 'n kreatiniensuiwering van minder as 50 ml/min, was die K_{maks} en $AOK_{0-\infty}$ van emtrisitabien en tenofovir groter (sien **KONTRA-INDIKASIES, WAARSKUWINGS, Niersuiwering**).

Pasiënte met ingekorte lewerfunksie
Efavirens:
Die farmakokinetika van efavirens is nie voldoende in pasiënte met ingekorte lewerfunksie bestudeer nie (sien **SPESIALE VOORSORGSMAATREËLS**).
Emtrisitabien:
Die farmakokinetika van emtrisitabien is nie in pasiënte met ingekorte lewerfunksie bestudeer nie; emtrisitabien word egter nie tot 'n beduidende mate deur lewerensieme gemetaboliseer nie. Derhalwe behoort die impak van ingekorte lewerfunksie minimaal te wees.
Tenofovirdisoproksielfumaraat:
Die farmakokinetika van tenofovir na 'n 300 mg dosis van tenofovir DF is in nie-MIV besmette pasiënte met matig tot erg ingekorte lewerfunksie bestudeer. In vergelyking met nie-ingekorte lewerfunksie was daar geen noemenswaardige veranderinge in die farmakokinetika van tenofovir in pasiënte met ingekorte lewerfunksie nie.

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

KONTRA-INDIKASIES:
TRIOLAR TABLETTE word teenaangedui:
- In pasiënte wat voorheen hipersensitiwiteit teen emtrisitabien, tenofovir of efavirens of enige van die ander komponente van die middel getoon het.
- In pasiënte met matig tot erg ingekorte nierfunksie (kreatiniensuiwering <50 ml/min) (Sien **WAARSKUWINGS** en **DOSIS EN GEBRUIKSAANWYSINGS**).
- In pasiënte wat terselfdertyd behandeling met astemisool, kisapried, midasolam, triasolam of ergotderivate ontvang, aangesien kompetisie vir CYP3A4 deur die efavirens in **TRIOLAR TABLETTE** tot 'n inhibisie van die metabolisme van hierdie medisyne mag lei en die potensiaal vir ernstige en/of lewensbedreigende newe-effekte mag veroorsaak (bv. hartdisritmieë, verlengde sedering of respiratoriese onderdrukking).
- In pasiënte wat terselfdertyd vorikonasool gebruik, aangesien efavirens die plasmakonsentrasies van vorikonasool aansienlik verlaag, terwyl vorikonasool die plasmakonsentrasies van efavirens aansienlik verhoog. Aangesien **TRIOLAR TABLETTE** 'n vastedosis kombinasie is, kan die efavirens dosis nie verander word nie. Daarom moet vorikonasool en **TRIOLAR TABLETTE** nie saam toegedien word nie.
- In pasiënte wat swanger is of borsvoed (sien **SWANGERSKAP EN LAKTASIE**).

WAARKUWINGS:
Melksuurasidose / Erge hepatomegalie met steatose:
Melksuurasidose en erge hepatomegalie met steatose, insluitende fatale gevalle, is met die gebruik van nukleosiedanaloë, alleen of in kombinasie met ander antiretrovirusmiddels aangemeld. Die meerderheid van hierdie gevalle was in vroue. Vetsug en verlengde nukleosiedblootstelling mag risikofaktore wees. Sorg behoort veral aan die dag gelê te word wanneer nukleosiedanaloë aan enige pasiënt met bekende risikofaktore vir lewersiekte toegedien word. Gevalle is egter ook aangemeld in pasiënte met geen bekende risikofaktore nie. Die behandeling met **TRIOLAR TABLETTE** behoort opgeskort te word in enige pasiënt wat kliniese of laboratoriumbevindings ontwikkel wat op melksuurasidose of uitgesproke hepatotoksisiteit (wat hepatomegalie en steatose, selfs in die afwesigheid van merkbare verhogings in transaminase mag insluit) dui.

Pasiënte wat met beide MIV en hepatitis B virus besmet is:
Dit word aanbeveel dat alle pasiënte met MIV vir die teenwoordigheid van hepatitis B virus (HBV) getoets word voor inisiëring van terapie met antiretrovirusmiddels. **TRIOLAR TABLETTE** word nie vir die behandeling van chroniese HBV infeksie aanbeveel nie en die veiligheid en effektiwiteit van **TRIOLAR TABLETTE** is nie in pasiënte wat met beide HBV en MIV besmet is, bevestig nie. Erge akute verergerings van hepatitis het in pasiënte voorgekom na die staking van emtrisitabien en tenofovirdisoproksielfumaraat**.** Pasiënte wat met beide HBV en MIV besmet is en wat met die gebruik van **TRIOLAR TABLETTE** staak, vereis noukeurige monitering van hul lewerfunksie vir ten minste etlike maande; dit sluit beide kliniese en laboratoriumopvolg in. Toepaslike inisiëring van antihepatitis B terapie mag nodig wees.

Medetoediening met verwante medisyne
Verwante medisyne wat nie saam met **TRIOLAR TABLETTE** toegedien moet word nie sluit die volgende in: emtrisitabien, tenofovir DF, emtrisitabien/tenofovir DF en efavirens, wat dieselfde komponente as **TRIOLAR TABLETTE** bevat. Weens die ooreenkoms tussen emtrisitabien en lamivudien, behoort **TRIOLAR TABLETTE** 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 aktiewe bestanddele van **TRIOLAR TABLETTE**, word hoofsaaklik deur die niere opgeruim. **TRIOLAR TABLETTE** behoort nie aan pasiënte met 'n kreatiniensuiwering van <50 ml/min toegedien te word nie.
Daar bestaan vermeldings van ingekorte nierfunksie, insluitende gevalle van akute nierversaking en Fanconi se sindroom (nierbuisbesering met erge hipofosfatemie) in assosiasie met die gebruik van tenofovir DF (sien **Newe-effekte**).
Dit word aanbeveel dat kreatiniensuiwering in alle pasiënte, vóór en waar klinies nodig, gedurende terapie met **TRIOLAR TABLETTE** bereken moet word. Roetine monitering van berekende kreatiniensuiwering en serumfosfaat behoort in pasiënte met die risiko vir ingekorte nierfunksie uitgevoer te word.
Die gebruik van **TRIOLAR TABLETTE** behoort in pasiënte wat terselfdertyd of onlangs 'n nefrotoksiese middel gebruik/gebruik het, vermy te word.

***Interaksie met ander medisyne* (sien INTERAKSIES).**
Die gelyktydige gebruik van **TRIOLAR TABLETTE** 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 NNTTIs, insluitende efavirens saam met St. John se kruid 'n aansienlike afname in die NNTTi-konsentrasies sal veroorsaak. Dit mag tot sub-optimale efavirensvlakke, met die gevolglike verlies aan virologiese respons en moontlike weerstand teen efavirens, of tot die klas van NNTTi lei.

Psigiatriese simptome
Ernstige psigiatriese newe-effekte is in pasiënte wat met efavirens behandel is, aangemeld. In gekontroleerde proewe in pasiënte wat met efavirensbevattende regimens, behandel is, was die frekwensie van spesifieke ernstige psigiatriese newe-effekte in pasiënte wat efavirens- of kontroleregimens ontvang het, respektiewelik: erge depressie (2,4 %, 0,9 %), selfmoordidees (0,7 %, 0,3 %), nie-fatale selfmoordpogings (0,5 %, 0 %), aggressiewe gedrag (0,4 %, 0,5 %), paranoïese reaksies (0,4 %, 0,3 %) en maniese reaksie (0,2 %, 0,3 %). Wanneer psigiatriese simptome soortgelyk aan dié hierbo genoem, gekombineer en as 'n groep in 'n multifaktoriale ontleding van data geëvalueer is, was die behandeling met efavirens geassosieer met 'n toename in die voorkoms van hierdie geselekteerde psigiatriese simptome. Ander faktore wat met 'n toename in die voorkoms van hierdie psigiatriese simptome geassosieer is, was 'n geskiedenis van inspuitbare middelgebruik, 'n 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 efavirensbehandelde indiwidue het die behandeling weens een of meer van hierdie geselekteerde psigiatriese newe-effekte 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 bepaal word nie. Pasiënte met ernstige psigiatriese newe-effekte behoort onmiddellik mediese evaluering te ondergaan om die moontlikheid dat die simptome met die gebruik van efavirens verband hou, te bepaal. Indien wel, behoort die risiko van voortgesette terapie teenoor die voordele opgeweeg te word (sien **NEWE-EFFEKTE EN SPESIALE VOORSORGSMAATREËLS**).

Senuweestelselsimptome
53 % van pasiënte wat efavirens in gekontroleerde studies ontvang het, het simptome van die sentrale senuweestelsel aangemeld, in teenstelling met 25 % van pasiënte wat die kontroleregimens ontvang het. Hierdie simptome het duiseligheid (28,1 %), slaaploosheid (16,3 %), ingekorte konsentrasie (8,3 %), slaapsug (7,0 %), abnormale drome (6,2 %) en hallusinasies (1,2 %) ingesluit. Ander aangemelde simptome was euforie, verwardheid, agitasie, geheueverlies, bedwelming, abnormale denke en depersonalisering ingesluit. Die meerderheid van hierdie simptome was gering tot matig (50,7 %); die simptome was erg in 2,0 % van indiwidue. Oor die algemeen het 2,1 % van die indiwidue as gevolg hiervan terapie 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 ten minste matige aard van die senuweestelsel gewissel van 5 % tot 9 % in die indiwidue wat met die efavirensbevattende regimens behandel is, en in 3 % tot 5 % in die indiwidue wat met die kontroleregimen behandel is. Pasiënte behoort ingelig te word dat hierdie algemene simptome waarskynlik met voortgesette terapie sal verbeter en dat hulle nie voorspellend van daaropvolgende aanvangs van minder dikwels voorkomende psigiatriese simptome is nie. Dosering met slapenstyd mag die verdraagsaamheid van hierdie simptome van die senuweestelsel verbeter.
Pasiënte wat **TRIOLAR TABLETTE** ontvang, behoort bewus gemaak te word van die potensiaal vir bykomende simptome van die senuweestelsel wanneer **TRIOLAR TABLETTE** saam met alkohol of psigo-aktiewe medisyne gebruik word.
Pasiënte wat simptome van die sentrale senuweestelsel soos duiseligheid, ingekorte konsentrasie en/of lomerigheid ondervind, behoort potensieel gevaarlike take soos om 'n motor te bestuur of met masjinerie te werk, te vermy.

INTERAKSIES
Efavirens:
Dit is *in vivo* aangetoon dat efavirens CYP3A4 induseer. Die plasmakonsentrasies van ander verbindings wat substrate van CYP3A4 is, mag afneem wanneer hulle saam met efavirens toegedien word. *In vitro* studies het aangetoon dat efavirens 2C9, 2C19 en 3A4 isoënsieme in die reikwydte van waargenome efavirens plasmakonsentrasies inhibeer. Die medetoediening van efavirens saam met medisyne wat hoofsaaklik deur hierdie isoënsieme gemetaboliseer word, mag tot veranderde plasmakonsentrasies van hierdie middels lei.
Daar word verwag dat medisyne wat CYP3A4-aktiwiteit induseer (bv. fenobarbital, rifampien, rifabutien), die suiwering van efavirens sal verhoog, wat tot laer plasmakonsentrasies lei.

Emtrisitabien en tenofovirdisoproksielfumaraat:
Aangesien emtrisitabien en tenofovir hoofsaaklik deur die niere opgeruim word, mag die medetoediening van **TRIOLAR TABLETTE** saam met medisyne wat nierfunksie verminder of met aktiewe buissekresie kompeteer, die serumkonsentrasies van emtrisitabien, tenofovir en/of ander medisyne wat deur die niere uitgeskei word, verhoog. Sommige voorbeelde is asiklovir, adefovirdipivoksiel, sidofovir, gansiklovir, valasiklovir en valgansiklovir, 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. Die gebruik van didanosien behoort gestaak te word in pasiënte wat didanosienverwante newe-effekte ontwikkel (Sien tabel 3 vir aanbevelings ten opsigte van die aanpassing van didanosiendosering). Onderdrukking van die CD4 seltellings is in pasiënte wat tenofovir DF met 400 mg didanosien daagliks ontvang, waargeneem.
Dit is aangetoon dat atasanavir en lopinavir/ritonavir die konsentrasies van tenofovir verhoog. Die meganisme van hierdie interaksie is onbekend. Hoër tenofovirkonsentrasies mag moontlik tenofovirgeassosieerde newe-effekte potensieer, insluitende nierafwykings. Pasiënte wat atasanavir of lopinavir/ritonavir saam met tenofovir DF ontvang, behoort vir tenofovirgeassosieerde newe-effekte gemonitor te word. Die gebruik van **TRIOLAR TABLETTE** behoort gestaak te word in pasiënte wat tenofovirgeassosieerde newe-effekte ontwikkel (Sien Tabel 3 vir aanbevelings ten opsigte van die aanpassing van atasanavirdosering).
Inligting oor ander belangrike medisyne interaksies vir **TRIOLAR TABLETTE** word in Tabel 2 en 3 opgesom. Die interaksies wat beskryf word, is gebaseer op studies uitgevoer met efavirens, emtrisitabien of tenofovir DF as indiwiduele middels of is potensiële medisyne interaksies. Geen medisyne interaksiestudies is met **TRIOLAR TABLETTE** uitgevoer nie. Die tabelle sluit potensieel beduidende interaksies in, maar is nie volledig nie.

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

Klas van medisyne Naam van medisyne	**Kliniese kommentaar**
Swamwerend: vorikonasool	TEENAANGEDUI aangesien efavirens die plasmakonsentrasies van vorikonasool aansienlik verlaag en die medetoediening die terapeutiese effektiwiteit van vorikonasool verminder. Boonop verhoog vorikonasool die plasmakonsentrasies van efavirens aansienlik wat die risiko van efavirensverwante newe-effekte mag verhoog
Antihistamien: astemisool	TEENAANGEDUI weens die potensiaal vir ernstige en/of lewensbedreigende reaksies soos hartaritmieë
Antimigraine: ergotderivate (dihidroërgotamien, ergonovien, ergotamien, metielergonovien)	TEENAANGEDUI weens die potensiaal vir ernstige en/of lewensbedreigende reaksies, soos akute ergotvergiftiging wat deur perifere vasospasme en isgemie van die ledemate en ander weefsels gekenmerk word.
Antiretrovirusmiddels: efavirens, emtrisitabien, tenofovir DF, lamivudien	Nie vir gebruik saam met **TRIOLAR TABLETTE** nie weens die aktiewe bestanddele – emtrisitabien, tenofovir DF emtrisitabien/tenofovir DF en efavirens is komponente van **TRIOLAR TABLETTE**. Lamivudien is soortgelyk aan emtrisitabien.
Bensodiasepiene: midasolam, triasolam	TEENAANGEDUI weens die potensiaal vir ernstige en/of lewensbedreigende reaksies soos 'n verlenging of toename in sedering of respiratoriese onderdrukking
Kalsiumkanaalblokkeerders: bepridiel	TEENAANGEDUI weens die potensiaal vir ernstige en/of lewensbedreigende reaksies soos hartaritmieë.
GI bewegingsmiddel: kisapried	TEENAANGEDUI weens d ie potensiaal vir ernstige en/of lewensbedreigende reaksies soos hartaritmieë.
Neuroleptika: pimosied	TEENAANGEDUI weens die potensiaal vir ernstige en/of lewensbedreigende reaksies soos hartaritmieë.
St. John se kruid *(Hypericum perforatum)*	NIE AANBEVEE L NIE: Daar word verwag dat dit die plasmavlakke van efavirens aansienlik sal laat afneem; is nie in kombinasie met efavirens bestudeer nie.

Tabel 3: Bevestigde en ander potensieel beduidende[1] medisyne interaksies: Verandering van dosis of regimen mag, gebaseer op medisyne interaksieproewe of voorspelde interaksie aanbeveel word.

Klas meegaande medisyne: Naam van 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): Ten opsigte van veiligheid en effektiwiteit is toepaslike dosisse van fosamprenavir saam met **TRIOLAR TABLETTE** nie vasgestel nie. Bykomende 100 mg per dag ritonavir (totaal 300 mg) word aanbeveel wanneer **TRIOLAR TABLETTE** saam met fosamprenavir een keer per dag toegedien word. Geen verandering is in die ritonavirdosis nodig wanneer **TRIOLAR TABLETTE** saam met fosamprenavir/ritonavir een keer per dag toegedien word nie. Geen verandering is in die ritonavird osis nodig wanneer **TRIOLAR TABLETTE** saam met fosamprenavir plus ritonavir twee keer per dag toegedien word nie.
Proteaseïnhibeerder: Atasanavir	↓ atasanavir-konsentrasie ↑ tenofovir-konsentrasie	Die plasmakonsentrasie van atasanavir word deur beide efavirens en tenofovir DF verlaag. Daar bestaan nie voldoende data om 'n doseringsaanbeveling vir atasanavir of atasanavir/ritonavir saam met **TRIOLAR TABLETTE** te maak nie. Daarom word die medetoediening van **TRIOLAR TABLETTE** en atasanavir nie, weens die besorgdheid oor 'n afname in die atasanavirkonsentrasie, aanbeveel nie.
Proteaseïnhibeerder: Indinavir	↓ indinavir-konsentrasie	Die optimale indinavirdosis, wanneer saam met efavirens toegedien word, is nie bekend nie. Verhoging van die indinavirdosis na 1000 mg elke 8 ure kompenseer nie vir die toename in metabolisme van indinavir weens efavirens nie.
Proteaseïnhibeerder: Lopinavir/ritonavir	↓lopinavir-konsentrasie ↑ tenofovir-konsentrasie	'n Dosistoename vir lopinavir/ritonavir na 600/150 mg (3 tablette) keer per dag mag oorweeg word wanneer in kombinasie met efavirens in behandelingservare pasiënte in wie 'n afname in die vatbaarheid vir lopinavir vermoed word (deur behandelings - geskiedenis of laboratoriumbewys). **Pasiënte behoort vir tenofovirverwante newe-effekte gemonitor te word. TRIOLAR TABLETTE behoort in pasiënte wat tenofovirverwante newe-effekte ontwikkel, onttrek te word.**
Proteaseïnhibeerder: Ritonavir	↑ ritonavir-konsentrasie ↓efavirens-konsentrasie	Nadat ritonavir 500 mg elke 12 ure saam met efavirens 600 mg een keer per dag toegedien is, was die kombinasie geassosieer met 'n hoër frekwensie van kliniese newe-effekte (bv.duiseligheid, naarheid, pareste sie) en laboratorium-abnormaliteite (verhoogde lewer-ensieme). Die monitering van lewerensieme word aanbeveel wanneer **TRIOLAR TABLETTE** in kombinasie met ritonavir gebruik word.
Proteaseïnhibeerder: Sakinavir	↑ sakinavir-konsentrasie	Behoort nie as 'n enkel proteaseïnhibeerder in kombinasie met **TRIOLAR TABLETTE** gebruik te word nie.
NTTI: Didanosien	↑ didanosien-konsentrasie	Hoër didanosienkonsentrasies mag didanosienverwante newe-effekte potensieer, insluitende pankreatitis en neuropatie. **In volwassenes wat meer as 60 kg weeg, behoort die didanosiendosis na 250 mg verminder te word wanneer dit saam met TRIOLAR TABLETTE toegedien word. Daar is geen data beskikbaar om 'n dosisaanpassing vir pasiënte wat minder as 60 kg weeg, aan te beveel nie.** Wanneer saam toegedien word, mag **TRIOLAR TABLETTE** en didanosien onder vastende kondisies of saam met 'n ligte maaltyd (minder as 400 kkal, 20% vet) geneem word. Die medetoediening van didanosien gebufferde formulasie saam met **TRIOLAR TABLETTE** behoort onder vastende kondisies te geskied. **Die medetoediening van TRIOLAR TABLETTE en didanosien behoort noukeurig vir didanosienverwante newe-effekte gemonitor te word.**
Ander middels		
Antistolmiddel: Warfarien	↑ of ↓ warfarien-konsentrasie	Plasmakonsentrasies en effekte word potensieel deur efavirens verhoog of verlaag
Antistuipmiddels: Karbamasepien	↓karbamasepien-konsentrasie ↓efavirens-konsentrasie	Daar is te min data beskikbaar om 'n dosisaanbeveling vir **TRIOLAR TABLETTE** te maak. Alternatiewe antistuipbehandeling behoort gebruik te word.
Fenitoïen Fenobarbital	↓konsentrasie van antikonvulsiewe middel ↓efavirens-konsentrasie	Potensiaal vir 'n afname in antistuipmiddel- en/of plasmakonsentrasies van efavirens. Periodieke monitering van die plasmavlakke van die antistuipmiddel behoort uitgevoer te word.
Antidepressante: Sertralien	↓sertralien-konsentrasie	Toenames in die sertraliendosis behoort deur die kliniese respons gelei te word.
Swamwerende middels: Intrakonasool	↓itrakonasool-konsentrasie ↓Hidroksi-itrakonasool-konsentrasie	Aangesien geen dosisaanbeveling vir itrakonasool gemaak kan word nie, behoort alternatiewe swamwerende behandeling oorweeg te word.
Ketokonasool	↓ketokonasool-konsentrasie	Interaksiestudies met **TRIOLAR TABLETTE** en ketokonasool is nie uitgevoer nie. Efavirens besit die potensiaal om die plasmakonsentrasies van ketokonasool te verlaag
Anti-infektief: Klaritromisien	↓klaritromisien-konsentrasie ↑ 14-OH metaboliet konsentrasie	Die kliniese betekenis is onbekend. In onbesmette vrywilligers het 46 % 'n uitslag ontwikkel terwyl hulle efavirens en klaritromisien gebruik het. Geen dosisaanpassing word aanbeveel wanneer **TRIOLAR TABLETTE** saam met klaritromisien toegedien word nie. 'n Alternatief vir klaritromisien, soos azitromisien behoort oorweeg te word. Ander makroliede antibiotika, soos eritromisien is nie in kombinasie met **TRIOLAR TABLETTE** bestudeer nie.
Antimikobakterieel: Rifabutien	↓rifabutien-konsentrasie	Verhoog die daaglikse rifabutiendosis met 50 %. Oorweeg verdubbeling van die rifabutien -dosis in regimens waar rifabutien 2 of 3 keer per week toegedien word.
Antimikobakterieel: Rifampisien	↓efavirens-konsentrasie	Die kliniese betekenis van 'n verlaagde efavirenskonsentrasies is nie bekend nie. Dosis-aanbevelings vir die gelyktydige gebruik van **TRIOLAR TABLETTE** en rifampisien is nie vasgestel nie.
Kalsiumkanaal-blokkeerders: Diltiasem	↓diltiasem-konsentrasie ↓desasetiel-diltiasem konsentrasie	Aanpassing van die diltiasemdosis behoort deur die kliniese respons gelei te word.Geen dosisaanpassing is nodig wanneer **TRIOLAR TABLETTE** saam met diltiasem toegedien word nie.
Ander (bv. felodipien, nifedipien, nikardepien, verapamiel)	↓monodesmetiel-diltiasem konsentrasie ↓kalsiumkanaal-blokkeerder	Geen data is beskikbaar oor die potensiële interaksies van efavirens met ander kalsiumka naalblokkeerders wat substrate vir CYP3A4 is nie. Daar bestaan 'n potensiaal vir die afname in plasmakonsentrasies van die kalsiumkanaalblokkeerder. Dosisaanpassing behoort deur die kliniese respons gelei te word.
HMG-KoA reduktaseïnhibeerders: Atorvastatien, Pravastatien Simvastatien	↓atorvastatien-konsentrasie ↓pravastatien-konsentrasie ↓simvastatien-konsentrasie	Die plasmakonsentrasies van atorvastatien, pravastatien en simvastatien het met efavirens afgeneem. Raadpleeg die volledige voubiljette van die HMG -KoA reduktaseïnhibeerder vir riglyne oor indiwiduele dosisse.
Narkotiese pynstiller: Metadoon	↓metadoon-konsentrasie	Die medetoediening van efavirens in MIV -1 indiwidue met 'n geskiedenis van die gebruik van inspuitbare medisyne het tot 'n afname in die plasmavlakke van metadoon en tekens van opioïedonttrekking gelei. Die metadoondosis is met 'n gemiddeld van 22% verhoog om die onttrekkingsimptome te verlig. Pasiënte behoort vir tekens van onttrekking gemonitor te word en hul metadoondosis behoort waar nodig verhoog word om die onttrekkingsimptome te verlig.
Orale voorbehoedmiddels: Etinielestradiol	↑ etinielestradiol-konsentrasie	Die kliniese betekenis is onbekend. Aangesien die potensiële interaksie van efavirens met orale voorbehoedmiddels nie ten volle gekenmerk is nie, behoort 'n betroubare vorm van skeidingskontrasepsie bo en behalwe die orale voorbehoedmiddels gebruik te word.

[1] Hierdie tabel is nie volledig nie

Interferensie met efavirensontleding
Kannabinoïed toetsinteraksie:
Efavirens bind nie kannabinoïedreseptors nie. Vals-positiewe kannabinoïed urientoetsresultate is in nie-MIV-besmette vrywilligers wat efavirens ontvang het waargeneem wanneer die Microgenics Cedia DAU Multi-Level THC bepaling vir sifting gebruik is. Negatiewe resultate is verkry wanneer meer spesifieke bevestigende toetse met gaschromatografie/massaspektrometrie gebruik is.

Ander interaksies:
Efavirens:
Interaksiestudies is met efavirens en ander medisyne wat moontlik saam toegedien word of met medisyne wat dikwels as voelers vir farmakokinetiese interaksie gebruik word, uitgevoer. Geen klinies betekenisvolle interaksie is tussen efavirens en sidovudien, lamivudien, asitromisien, flukonasool, lorasepam, sertresien of paroksetien waargeneem nie.
Enkel dosis famotidien of 'n aluminium- en magnesiumteensuurmiddel met simetikoon het geen effek op efavirens gehad nie.

Emtrisitabien en tenofovirdisoproksielfumaraat:
Geen klinies betekenisvolle medisyne interaksies is tussen emtrisitabien en tenofovir, indinavir, stavudien, tenofovir DF en sidovudien waargeneem nie. Netso is geen klinies betekenisvolle interaksies tussen tenofovir DF en abasavir, adefovir, dipivoksiel, efavirens, emtrisitabien, indinavir, lamivudien, lopinavir/ritonavir, metadoon, nelfinavir, orale voorbehoedmiddels, ribavirin en sakinavir/ritonavir in studies in gesonde vrywilligers 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 tenofovirfarmakokinetika soortgelyk aan dié wat in vorige studies waargeneem is. Dit dui op 'n tekort aan klinies betekenisvolle medisyne interaksies tussen hierdie middels en tenofovir DF.

SWANGERSKAP EN LAKTASIE:
Die gebruik van **TRIOLAR TABLETTE** word gedurende swangerskap teenaangedui aangesien die veiligheid en effektiwiteit nie vasgestel is nie (sien **KONTRA-INDIKASIES**).
Skeidingskontrasepsie behoort altyd in kombinasie met ander voorbehoedmiddels gebruik te word (bv. orale of ander hormonale voorbehoedmiddels).
Vroue wat swanger mag raak behoort 'n swangerskaptoets vir die inisiëring van behandeling met **TRIOLAR TABLETTE** te ondergaan (sien **KONTRA-INDIKASIES**).

Borsvoeding: MIV-besmette moeders behoort nie hul babas te borsvoed nie. Dit is nie bekend of efavirens, emtrisitabien of tenofovir in menslike melk uitgeskei word nie. Weens die potensiaal vir MIV-oordrag, asook die potensiaal vir ernstige newe-effekte in babas wat boersvoeding kry, **behoort moeders aangesê te word om nie te borsvoed wanneer hulle TRIOLAR TABLETTE gebruik nie.**

DOSIS EN GEBRUIKSAANWYSINGS:
Volwassenes:
Die aanbevole dosis van **TRIOLAR TABLETTE** is een tablet oraal een keer per dag.
TRIOLAR TABLETTE behoort op 'n leë maag geneem te word, aangesien voedsel die efavirensblootstelling mag verhoog, wat tot 'n toename in die frekwensie van newe-effekte mag lei. Om die verdraagsaamheid tot efavirens ten opsigte van die ongewenste effekte op die senuweestelsel te verbeter, word dit aanbeveel dat **TRIOLAR TABLETTE** saans met slapenstyd geneem word.

Kinders en adolessente:
Weens die tekort aan data oor die veiligheid en effektiwiteit van **TRIOLAR TABLETTE**, word dit nie vir gebruik in kinders jonger as 18 jaar oud aanbeveel nie (sien **KONTRA-INDIKASIES**).

Ingekorte nierfunksie:
TRIOLAR TABLETTE word nie aanbeveel vir pasiënte met matig tot erg ingekorte nierfunksie nie (kreatiniensuiwering <50 ml/min).

NEWE-EFFEKTE EN SPESIALE VOORSORGSMAATREËLS:
Newe-effekte:
Efavirens (600 mg):
Metabolisme en voedingsafwykings:
Frekwensie onbekend: Gewigstoename of –verlies, herverspreiding/akkumulasie van liggaamsvet, hipercholesterolemie, hipertrigliseridemie.
Psigiatriese afwykings:
Minder dikwels: Bedwelming, verwardheid, ingekorte konsentrasie, slaaploosheid, angs, abnormale drome, depressie, abnormale denke, agitasie, delirium, emosionele onstabiliteit, euforie, hallusinasies, psigose.
Frekwensie onbekend: Delusies, ongewone gedrag, erge akute depressie (insluitende selfmoordidees of-pogings), neurose, paranoïe, apatie, manie.
Afwykings van die senuweestelsel:
Dikwels: Duiseligheid, hoofpyn, slaapsug.
Minder dikwels: Abnormale koördinasie ataksie, stuiptrekkings, migraine hoofpyne, neuralgie, parestesie, perifere neuropatie, spraakafwyking, bewerasie, hipoëstesie.
Oogafwykings:
Minder dikwels: Abnormale gesig.
Afwykings van die oor en labirint:
Minder dikwels: Tinnitus, vertigo.
Hartafwykings:
Minder dikwels: Warmgloede, hartkloppings en tagikardie.
Respiratoriese, bors- en mediastinale afwykings:
Minder dikwels: Asma, boonste lugweginfeksies, sinusitis.
Frekwensie onbekend: Dispnee.
Gastroïntestinale afwykings:
Dikwels: Naarheid, braking, diaree.
Minder dikwels: Gastritis, gastroënteritis, gastroësofagale refluks, toename in eetlus, smaakversteuring.
Frekwensie onbekend: Hardlywigheid, wanabsorpsie.
Hepatobileêre afwykings:
Minder dikwels: Hepatitis.
Frekwensie onbekend: Toename in lewerensieme, lewerversaking.
Afwykings van die vel en subkutane weefsels:
Dikwels: Diffuse makulopapulêre uitslag
Minder dikwels: Erge uitslag met geassosieerde blasievorming, vogtige afskilfering of ulkusse, aknee, alopesie, ekseem, follikulitis, seboree, velskilfering, urtikarie.
Frekwensie onbekend:
Warmgloede, erythema multiforme, naelafwykings, fotoallergiese 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 afwykings by die plek van toediening:
Dikwels: Moegheid
Minder dikwels: Astenie, malaise, pyn, sinkopee, griepagtige simptome, alkoholintoleransie, warmgloede.

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), depressiewe afwyking.
Gastroïntestinale afwykings:
Dikwels: Naarheid, braking, diaree.
Frekwensie onbekend: Buikpyn, dispepsie.
Afwykings van die vel en subkutane weefsel:
Dikwels: Uitslagepisodes (insluitende uitslag, pruritus, makulopapulêre uitslag, urtikarie, vesikulobulleuse uitslag, pustulêre uitslag en allergiese reaksie).
Frekwensie onbekend: Velverkleuring, gemanifesteer deur hiperpigmentasie op die handpalms en/of voetsole.
Muskuloskeletale, bindweefsel- en beenafwykings:
Frekwensie onbekend: Artralgie, mialgie.
Afwykings van die bloed- en limfsisteem:
Frekwensie onbekend: Neutropenie, anemie.
Nier- en urienafwykings:
Dikwels: Verhoging van kreatinienkinase.***Respiratoriese, bors- en mediastinale afwykings:***
Frekwensie onbekend: Toename in hoes en rinitis.
Hepatobileêre afwykings:
Frekwensie onbekend: Verhoogde lewerensiemkonsentrasies en hiperbilirubinemie.
Metabolisme en voedingsafwykings:
Frekwensie onbekend: Melksuurasidose, gewoonlik geassosieer met erge hepatomegalie en steatose, hipertrigliseridemie, hiperglukemie.

TENOFOVIR (300 mg):
Gastroïntestinale afwykings:
Dikwels: Naarheid, braking, diaree, buikpyn, winderigheid, dispepsie en anoreksie.
Minder dikwels: Verhoogde serumamilasekonsentrasies, 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 weefsel:
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.
Metabolisme en voedingsafwykings:
Dikwels: Hipofosfatemie.
Frekwensie onbekend: Melksuurasidose, gewoonlik geassosieer met erge hepatomegalie en steatose, hipertrigliseridemie, hiperglukemie.
Nier- en urienafwykings:
Frekwensie onbekend: Verhoging in kreatinienkinasevlakke, nefritis, nefrogeniese diabetes insipidus, ingekorte nierfunksie, akute nierversaking, effekte op die proksimale nierbuisies, insluitende Fanconi se sindroom, nierversaking, proksimale tubulopatie, proteïnurie, akute buisnekrose.
Afwykings van die immuunstesel:
Frekwensie onbekend: Allergie, allergiese reaksies.
Algemene afwykings:
Frekwensie onbekend: Koors, sweet, gewigsverlies.

Spesiale voorsorgsmaatreëls:
Melksuurasidose / erge hepatomegalie met steatose:
Roetinetoetsing van serumlaktaatvlakke in asimptomatiese pasiënte op ART word nie aanbeveel nie. Die bestuur van serumlaktaatvlakke word slegs aanbeveel vir pasiënte met kliniese tekens of simptome van melksuurasidose.
Laktaat 2 tot 5 mmol/l: monitor gereeld en wees attent op kliniese tekens.
Laktaat 5 tot 10 mmol/l sonder simptome: Monitor noukeurig.
Laktaat 5 tot 10 mmol/l met simptome: STAAK alle terapie, Sluit ander oorsake (bv. sepsis, uremie, diabetiese ketoasidose, tirotoksikose, limfoom) uit.
Laktaat meer of gelyk aan 10 mmol/l: STAAK alle terapie (80 % mortaliteit in gevallestudies).
Veluitslag:
Geringe tot matige uitslag, wat gewoonlik met voortgesette behandeling verdwyn, is met die gebruik van efavirens waargeneem. Behandeling met toepaslike antihistamiene en/of kortikosteroïede mag die verdraagsaamheid verbeter en verdwyning van die simptome versnel. Behandeling met **TRIOLAR TABLETTE** behoort gestaak te word in pasiënte wat erge uitslag wat met blasievorming, afskilfering, slymvliesbetrokkenheid en koors gepaardgaan, ontwikkel.
Senuweestelsel- en psigiatriese afwykings:
Daar bestaan vermeldings van senuweestelselsimptome met die gebruik van efavirens (sien **Newe-effekte**). Boonop is psigose-agtige reaksies, insluitende delusies en ongewone gedrag (insluitende aggressiewe reaksies) is ook aangemeld. Hierdie reaksies het hoofsaaklik in pasiënte met 'n geskiedenis van geestessiekte of middelmisbruik voorgekom. Daar bestaan 'n paar vermeldings van erge akute depressie (insluitende selfmoordidees en –pogings) in beide efavirensbehandelde en kontrolebehandelde pasiënte, veral in pasiënte met 'n vorige geskiedenis van depressie. Pasiënte behoort aangeraai te word om onmiddellik hul dokter te kontak indien hulle hierdie simptome ondervind, aangesien staking van **TRIOLAR TABLETTE** nodig mag wees.
Stuiptrekkings:
Stuiptrekkings is in mense wat efavirens gebruik, waargeneem, gewoonlik in die teenwoordigheid van 'n bekende geskiedenis van stuiptrekkings. Sorg moet in alle pasiënte met 'n geskiedenis van stuiptrekkings aan die dag gelê word.
Pasiënte wat terselfdertyd antikonvulsiewe medikasies wat hoofsaaklik deur die lewer gemetaboliseer word, soos fenitoïen en fenobarbital, mag periodieke monitering van plasmavlakke benodig.
Lewerensieme:
Die monitering van lewerensieme word aanbeveel in pasiënte met 'n bekende of vermoedelike geskiedenis van hepatitis B of C infeksie, asook in pasiënte wat met ander medisyne wat met lewertoksisiteit geassosieer word, behandel word. Die voordeel van voortgesette terapie met **TRIOLAR TABLETTE** moet teen die ongewenste risiko van aansienlike lewertoksisiteit in pasiënte wat aanhoudende verhogings in serumtransaminases van meer as 5 keer die boonste limiet van die normale reikwydte toon, opgeweeg word (sien **Newe-effekte**).
Cholesterol:
Die monitering van cholesterol- en trigliseriedvlakke behoort oorweeg te word in pasiënte wat met **TRIOLAR TABLETTE** behandel word (sien **Newe-effekte**).
Beeneffekte:
TRIOLAR TABLETTE verminder beenmineraaldigtheid. Beenmonitering behoort in MIV-besmette pasiënte met 'n geskiedenis van patologiese beenfraktuur of 'n risiko vir osteopenie oorweeg te word. Alhoewel die effek van aanvulling met kalsium en Vitamien D nie bestudeer is nie, mag hierdie aanvulling vir alle pasiënte voordelig wees. Indien beenabnormaliteite vermoed word, behoort die toepaslike konsultasie verkry te word.
Herverspreiding van vet:
Die herverspreiding/akkumulasie van liggaamsvet, insluitende sentrale vetsug, dorsoservikale vetvergroting (buffelskof), perifere vermaering, gesigsvermaering, borsvergroting en "cushingagtige voorkoms" is in pasiënte wat antiretrovirus terapie ontvang, aangemeld. Die meganisme en die langtermyn gevolge van hierdie gebeurtenisse is tans onbekend. 'n Oorsaaklike verwantskap is nie vasgestel nie.
Immuunherstelsindroom:
'n Immuunherstelsindroom is in pasiënte wat met kombinasie antiretrovirusterapie, insluitende **TRIOLAR TABLETTE** behandel is, aangemeld. Gedurende die aanvanklike fase van kombinasie antiretrovirusterapie, mag pasiënte wie se immuunstelsel reageer, 'n inflammatoriese respons teen trae of residueel opportunistiese infeksies (soos *Mycobacterium ovis* infeksie, sitomegalovirus, *pneumocystis jerovecci (carini)* pneumonie (PCP) of tuberkulose) ontwikkel, wat verdere evaluasie en behandeling mag vereis.
Pediatriese gebruik:
Die veiligheid en effektiwiteit van **TRIOLAR TABLETTE** in kinders is nie vasgestel nie.
Gebruik in bejaardes:
Kliniese studies met vaste dosis kombinasies van emtrisitabien en tenofovir, soos in **TRIOLAR TABLETTE** het nie 'n voldoende aantal indiwidue ouer as 65 jaar ingesluit om vas te stel of hulle anders as jonger indiwidue reageer nie. Oor die algemeen behoort sorg aan die dag gelê te word wanneer dosisse vir ouer pasiënte geselekteer word weens die groter frekwensie van 'n afname in lewer-, nier- en hartfunksie, asook meegaande siekte of medisinale terapie.
Opportunistiese infeksies:
Pasiënte wat **TRIOLAR TABLETTE** of enige ander antiretrovirus terapie gebruik mag aanhou om opportunistiese infeksies en ander komplikasies van MIV-infeksie op te doen. Hulle behoort daarom onder noulettende kliniese observasie gehou te word deur mediese praktisyns met ondervinding in die behandeling van pasiënte met MIV-verwante siektes.
Oordraging van MIV:
Pasiënte moet daaroor ingelig word dat daar geen bewys bestaan dat antiretrovirus terapieë, insluitende **TRIOLAR TABLETTE**, die risiko van oordraging van MIV na ander indiwidue deur seksuele kontak of bloedkontaminasie voorkom nie. Pasiënte behoort voort te gaan met die toepaslike voorsorgsmaatreëls.
Effek op die vermoë om te bestuur of om met masjinerie te werk:
Die gebruik van **TRIOLAR TABLETTE** mag tot duiseligheid, ingekorte konsentrasie en/of lomerigheid lei. Pasiënte behoort aangesê te word dat hulle, indien hulle hierdie simptome ontwikkel, potensieel gevaarlike take soos motor bestuur of met masjinerie te werk, behoort te vermy.

BEKENDE SIMPTOME VAN OORDOSERING EN BESONDERHEDE VAN DIE BEHANDELING DAARVAN:
In die geval van oordosering, moet die pasiënt vir bewys van toksisiteit gemonitor word en moet standaard ondersteunende behandeling, waar nodig toegedien word.
Efavirens:
Pasiënte wat per ongeluk 600 mg twee keer per dag geneem het, het 'n toename in senuweestelselsimptome en onwillekeurige spiersametrekkings aangemeld. Die behandeling van oordosering met efavirens behoort uit algemene ondersteunende maatreëls te bestaan. Dit behoort die monitering van lewenstekens en waarneming van die pasiënt se kliniese toestand in te sluit. Geaktiveerde houtskool mag toegedien word om te help met die verwydering van ongeabsorbeerde medisyne. Dit is onwaarskynlik dat dialise efavirens tot enige noemenswaardige mate uit die bloed sal verwyder, aangesien die medisyne hoogs proteïengebonde is.
Emtrisitabien:
Hemodialise verwyder ongeveer 30 % van die emtrisitabiendosis oor 'n 3-uur dialiseperiode, beginnende binne 1,5 ure na dosering met emtrisitabien (bloedvloeitempo van 400 ml/min en dialisaatvloei van 600 ml/min. Dit is nie bekend of emtrisitabien met peritoneale dialise verwyder kan word nie.
Tenofovirdisoproksielfumaraat:
Tenofovir word effektief deur hemodialise verwyder met n ekstraksiekoëffisiënt van ongeveer 54 %. Na 'n enkel 300 mg dosis van tenofovirdisoproksielfumaraat, verwyder 'n 4-uur hemodialisesessie ongeveer 10 % van die toegediende tenofovirdosis.

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

AANBIEDING:
HDPE houer:
Tablette word in 'n wit, ondeurskynende, ronde 120 ml HDPE houer met 'n 38 mm nek en 38 mm wit, ondeurskynende polipropileen geribde deksel en prop met induksiegeseëlde voering geseël. Elke houer bevat 28 of 30 tablette.

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

REGISTRASIENOMMER:
47/20.2.8/1006.

NAAM EN BESIGHEIDSADRES VAN DIE HOUER VAN DIE SERTIFIKAAT VAN REGSITRASIE:
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TRIOLAR TABLETTE

INLIGTINGSBLAADJIE VIR PASIËNTE

> Lees hierdie blaadjie noukeurig voordat u begin om **TRIOLAR TABLETTE** te gebruik
> - Hou hierdie blaadjie. U mag dit moontlik weer wil lees.
> - Indien u verdere vrae het, moet u asseblief u dokter of apteker raadpleeg.
> - **TRIOLAR TABLETTE** is vir u persoonlik voorgeskryf en u behoort dit nie met ander mense te deel nie. Dit mag hulle skade aandoen, ookal is hul simptome dieselfde.

S4

TRIOLAR TABLETTE (Filmbedekte tablette).
Efavirens, emtrisitabien en tenofovirdisoproksielfumaraat

WAT BEVAT TRIOLAR TABLETTE
Elke filmbedekte tablet bevat 600 mg efavirens, 200 mg emtrisitabien en 300 mg tenofovirdisoproksielfumaraat. Suikervry.
Ander bestanddele sluit mikrokristallyne sellulose, kroskarmellose natrium, hidroksipropielsellulose, natriumlourielsulfaat, magnesiumstearaat (plantaardige oorsprong), gepregelatiniseerde stysel, polivinielalkohol, titaniumdioksied (C.I. Nr. 77891), poliëtileenglikol, talkum, rooi ysteroksied (C.I. 77491) en swart ysteroksied (C.I. 77499) in.

WAARVOOR WORD TRIOLAR TABLETTE GEBRUIK
TRIOLAR TABLETTE word gebruik om menslike immuuntekrtvirus (MIV) infeksie in volwassenes te behandel. **TRIOLAR TABLETTE** word alleen, of in kombinasie met ander anti-MIV medisyne gebruik om pasiënte met MIV-1 infeksie te behandel.

VOORDAT U BEGIN OM TRIOLAR TABLETTE TE NEEM
Moenie TRIOLAR TABLETTE neem:
- As u hipersensitief (allergies) teen efavirens, emtrisitabien en tenofovirdisoproksielfumaraat, of enige van die ander bestanddele van **TRIOLAR TABLETTE** is.
- As u aan nierprobleme ly.
- As u swanger is of borsvoed.
- As u tans enige van die volgende medisyne neem:
  - Astemisool (gebruik om ander allergieë te behandel).
  - Kisapried (gebruik om sooibrand te behandel).
  - Bepridiel (gebruik om hartsiekte te behandel).
  - Ergotalkaloïede (bv. ergotamien, dihidroërgotamien, ergonovien en metielergonovien) (wat gebruik word om migraine en troshoofpyn te behandel).
  - Midasolam of triasolam (wat gebruik word om u te help slaap).
  - Pimosied (wat in sommige geesteskondisies gebruik word)
  - Vorikonasool (vir swaminfeksies).

Lig u dokter onmiddellik in as u enige van hierdie middels neem. Die neem van hierdie medisyne saam met **TRIOLAR TABLETTE** kan ernstige of lewensbedreigende newe-effekte veroorsaak of veroorsaak dat hierdie medisyne nie behoorlik werk nie.

Wees versigtig met TRIOLAR TABLETTE:

> **TRIOLAR TABLETTE mag tot ernstige probleme met u lewer lei en te veel suur in u liggaam veroorsaak. As dit nie behandel word nie, kan dit tot die dood lei. Die veiligheid en effektiwiteit van TRIOLAR TABLETTE in pasiënte wat met beide menslike immuuntekortvirus (MIV) en hepatitis B (HBV) besmet is, is nie vasgestel nie. TRIOLAR TABLETTE behoort nie vir die behandeling van chroniese HBV-infeksie gebruik te word nie. U behoort noukeurig deur u dokter gemonitor te word as u met HBV besmet is en die gebruik van TRIOLAR TABLETTE staak.**

- **TRIOLAR TABLETTE** mag melksuurasidose veroorsaak, wat gepaard gaan met 'n vergrootte lewer wat fataal kan wees. Diep, vinnige asemhaling, lomerigheid en simptome soos naarheid, braking en maagpyn mag op die ontwikkeling van melksuurasidose dui. Pasiënte wat oorgewig is loop 'n groter risiko.
- Lig u dokter in as u aan lewersiekte ly (insluitende hepatitis B). **TRIOLAR TABLETTE** behoort nie gebruik te word om chroniese hepatitis B virusinfeksie (HBV; 'n aanhoudende lewerinfeksie) te behandel nie. Onafhanklik van 'n geskiedenis van lewersiekte, sal u dokter gereelde bloedtoetse uitvoer om te bepaal hoe u lewer funksioneer.
- Lig u dokter in as u ander medisyne gebruik wat efavirens, emtrisitabien, of tenofovirdisoproksiel, of lamivudien of adefovirdipivoksiel bevat. **TRIOLAR TABLETTE** behoort nie met enige van hierdie medisyne geneem te word nie.
- Lig u dokter in as u aan 'n niersiekte gely het, of as toetse aangedui het dat u probleme met u niere het. **TRIOLAR TABLETTE** mag u niere affekteer.
- **TRIOLAR TABLETTE** word gewoonlik nie saam met ander medisyne wat u niere kan beskadig, geneem nie. Indien dit onafwendbaar is, sal u dokter u nierfunksie monitor.
- **TRIOLAR TABLETTE** mag uitslag veroorsaak. Indien u enige tekens van 'n erge uitslag met blaasvorming en koors waarneem, moet u die gebruik van **TRIOLAR TABLETTE** staak en onmiddellik u dokter raadpleeg.
- Lig u dokter in as u 'n geskiedenis van geestessiekte, insluitende depressie het, of as u aan substans- of alkoholmisbruik ly. Lig u dokter onmiddellik in as u depressief voel, as u selfmoordgedagtes huisves of as u aan vreemde dinge dink.
- Lig u dokter in as u aan stuiptrekkings ly of as u medisyne vir stuiptrekkings neem.
- **TRIOLAR TABLETTE** verminder die beenmineraaldigtheid wat tot frakture mag lei. U dokter mag kalsium en vitamien D supplemente voorskryf terwyl u **TRIOLAR TABLETTE** neem.
- **TRIOLAR TABLETTE** mag u liggaamsvorm verander deur die manier waarop vet in die liggaam versprei word, te verander. U mag vet van u bene, arms en gesig verloor en/of vet om die buikarea en interne organe aansit: u mag groter borste ontwikkel en vet op die rug en nek aansit (buffelskof).
- Indien u aan gevorderde MIV-infeksie ly (VIGS) en enige ander infeksie opdoen, mag u akute simptome van die infeksie of inflammasie ontwikkel, asook 'n agteruitgang van die simptome van 'n bestaande infeksie ondervind wanneer behandeling met **TRIOLAR TABLETTE** begin word. Indien u enige tekens van inflammasie of infeksie toon, of 'n agteruitgang daarvan ondervind, moet u onmiddellik u dokter raadpleeg.
- U sal **TRIOLAR TABLETTE** elke dag moet neem. **TRIOLAR TABLETTE** help om u kondisie te kontroleer en progressie van die siekte te vertraag. Dit is egter nie 'n kuur vir MIV-infeksie nie. U mag aanhou om ander infeksies en siektes wat met MIV-siekte gepaard gaan te ontwikkel. U behoort in gereelde kontak met u dokter te bly. Moenie ophou om die medisyne te gebruik voordat u nie u dokter geraadpleeg het nie.
- Daar is nie aangetoon dat **TRIOLAR TABLETTE** die risiko van die oordraging van MIV na ander deur onbeskermde seksuele kontak of bloedoordraging (bv. bloedoortappings en gemeenskaplike gebruik van naalde) verminder nie. U behoort die gepaste voorsorgsmaatreëls te tref om dit te voorkom.
- Die veiligheid en effektiwiteit van **TRIOLAR TABLETTE** in kinders en pasiënte jonger as 18 jaar oud is nie vasgestel nie.
- **TRIOLAR TABLETTE** word nie aanbeveel vir bejaardes ouer as 65 jaar nie.
- **TRIOLAR TABLETTE** mag bloedcholesterol, trigliseried- en suikervlakke verhoog en u dokter sal met gereelde tussenposes bloedtoetse uitvoer om u cholesterol, trigliseriede en suiker te monitor.

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

Swangerskap en borsvoeding:
- Moenie **TRIOLAR TABLETTE** neem as u swanger is nie. Misvorming is in fetusse van diere gesien wat tydens dragtigheid met **TRIOLAR TABLETTE** behandel is. Swangerskap behoort daarom in vroue wat **TRIOLAR TABLETTE** ontvang, vermy te word.
- Lig u dokter onmiddellik in as u swanger is of beoog om swanger te raak.
- Indien u 'n vrou is wat **TRIOLAR TABLETTE** ontvang, behoort 'n betroubare metode van skeidingskontrasepsie (bv. 'n kondoom) altyd saam met ander metodes van kontrasepsie, insluitende orale (die pil) of ander hormonale metodes van kontrasepsie (bv. implantate, inspuiting) gebruik te word.
- Moenie borsvoed as u **TRIOLAR TABLETTE** neem nie.

> As u swanger is of u borsvoed u baba terwyl u **TRIOLAR TABLETTE** neem, raadpleeg asseblief u dokter, apteker of ander gesondheidsorgbeampte.

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

Die neem van ander medisyne saam met TRIOLAR TABLETTE:

> **As u ander medisyne op 'n gereelde basis neem, insluitende komplementêre of tradisionele medisyne, kan die gebruik van TRIOLAR TABLETTE saam met hierdie medisyne ongewenste newe-effekte veroorsaak. Raadpleeg asseblief u dokter, apteker of ander gesondheidsorgbeampte vir advies.**

- Lig u dokter in as u enige ander medisyne gebruik of onlangs gebruik het.
- Lig u dokter in as u efavirens, abasavir, emtrisitabien, tenofovir, indinavir of lamivudien (vir MIV-besmetting) neem.
- As u enige van die volgende medisyne neem:
  - Astemisool (gebruik om hooikoors of ander allergieë te behandel).
  - Kisapried (gebruik om sooibrand te behandel).
  - Bepridiel (gebruik om hartsiektes te behandel).
  - Ergotalkaloïede (bv. ergotamien, dihidroërgotamien, ergonovien en metielergonovien) (gebruik om migraine en troshoofpyn te behandel).
  - Midasolam of triasolam (gebruik om u te help slaap).
  - Pimosied (gebruik om sekere geestesafwykings te behandel).
  - Vorikonasool (vir swaminfeksies).

As u enige van hierdie middels neem, lig asseblief u dokter onmiddellik in.

- Lig u dokter in as u atasanavir en/of lopinavir/ritonavir (vir MIV-besmetting) gebruik. As u enige van hierdie medisyne neem, mag dit vir u dokter nodig wees om u terapie meer noukeurig te monitor, of u mag moontlik nie **TRIOLAR TABLETTE** kan gebruik nie.
- Lig u dokter in as u ander medisyne neem wat didanosien (vir MIV-besmetting) neem. Die gebruik van **TRIOLAR TABLETTE** saam met ander antivirusmedisyne wat didanosien bevat, kan die didanosienvlakke in u bloed verhoog. Inflammasie van die pankreas en neuropatie (senuwee-afwykings) mag voorkom. U dokter sal dit noukeurig oorweeg om u met kombinasies van tenofovir en didanosien te behandel.
- Medisyne wat gebruik word om u bloedvette te verlaag (statiene): atorvastatien, pravastatien, simvastatien. **TRIOLAR TABLETTE** kan die hoeveelheid statiene in u bloed verlaag. U dokter sal u cholesterolvlakke nagaan en besluit om u statiendosis te verander, indien nodig.
- Medisyne wat gebruik word om stuiptrekkings (antikonvulsiewe medisyne) te behandel: Karbamasepien, fenitoïen, fenobarbital. **TRIOLAR TABLETTE** kan die hoeveelheid van die antikonvulsiewe middel in u bloed verminder. Karbamasepien kan die hoeveelheid efavirens, een van die bestanddele van **TRIOLAR TABLETTE**, in u bloed verminder. U dokter mag besluit om u antikonvulsiewe middel te verander.
- Medisyne wat gebruik word om bakteriese infeksies te behandel: Klaritromisien, rifabutien, rifampisien. U dokter mag besluit om die dosis te verander of 'n alternatiewe antibiotika voor te skryf. U dokter mag boonop besluit om u 'n bykomende dosis efavirens te geen om u MIV-besmetting te behandel.
- Medisyne wat gebruik word om swaminfeksies te behandel (swamweerders): itrakonasool of ketokonasool. **TRIOLAR TABLETTE** kan die hoeveelheid itrakonasool of ketokonasool in u bloed verminder. U dokter mag dit oorweeg om 'n ander swamweerder voor te skryf.
- Hormonale voorbehoedmiddels soos geboortebeperkingspille, 'n inspuitbare voorbehoedmiddel (bv. Depo-Provera) of implantaat: U behoort u betroubare skeidingsmetode van kontrasepsie soos 'n kondoom te gebruik, aangesien **TRIOLAR TABLETTE** hormonale voorbehoeding minder effektief mag maak.
- Metadoon, wat gebruik word om verslawing te behandel, aangesien u dokter moontlik u metadoondosis gaan verander.
- Sertralien, wat gebruik word om depressie te behandel, aangesien u dokter moontlik u sertraliendosis gaan verander.
- Diltiasem of soortgelyke medisyne (kalsiumkanaalblokkeerders): Wanneer u begin om **TRIOLAR TABLETTE** te neem, mag u dokter moontlik die dosis van u kalsiumkanaalblokkeerder aanpas.
- Warfarien (Medisyne wat gebruik word om bloedklonting te verminder): U dokter mag moontlik u warfariendosis aanpas.
- Daar word aanbeveel dat St. John se kruid (*Hypericum perforatum*), 'n kruiemiddel wat vir depressie gebruik word, nie saam met **TRIOLAR TABLETTE** geneem word nie.
- Lig u dokter in as u ander medisyne gebruik wat u nierfunksie affekteer. Sommige voorbeelde is:
  - 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)
  - Interleukien-2 (om kanker te behandel).

HOE OM TRIOLAR TABLETTE TE NEEM

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

- Bly onder u gesondheidsorgbeampte se sorg wanneer u **TRIOLAR TABLETTE** neem. Moenie die behandeling verander of staak voordat u nie u gesondheidsorgbeampte geraadpleeg het nie.
- Die normale **TRIOLAR TABLETTE** dosis is een tablet met water, een keer per dag met slapenstyd, sonder voedsel.

As u te veel TRIOLAR TABLETTE geneem het:
- Ontbied onmiddellik mediese hulp wanneer u vermoed dat u te veel **TRIOLAR TABLETTE** geneem het.

> **In die geval van oordosering, moet u u dokter of apteker raadpleeg. Indien hulle nie beskikbaar is nie, ontbied dan hulp by u naaste hospitaal of Gifbeheersentrum.**

As u vergeet het om u TRIOLAR TABLETTE te neem:
As u vergeet het om u dosis te neem, neem dit so gou as wat u daarvan onthou en gaan dan met die normale skedule voort. Moenie die dosis verdubbel om vir indiwiduele dosisse wat u vergeet het, op te maak nie.

MOONTLIKE NEWE-EFFEKTE:
TRIOLAR TABLETTE mag newe-effekte hê.
Ontbied nood mediese hulp as u enige van hierdie **tekens van 'n allergiese reaksie toon:**
- Velbulte; moeite met asemhaling; swelling van die gesig, lippe, tong of keel.

Ontbied onmiddellik u dokter as u enige van die volgende newe-effekte ondervind:
- Melksuurasidose (erge toename van melksuur in die bloed, 'n ernstige newe-effek wat fataal mag wees) – Die volgende newe-effekte is tekens van melksuurasidose: diep, vinnige asemhaling, lomerigheid, naarheid, braking, en maagpyn.
- Lewerbeskadiging – naarheid, maagpyn, lae koors, verlies aan eetlus, donker uriene, kleigekleurde stoelgang, geelsug (geel verkleuring van die vel of oë).
- Rugpyn veroorsaak deur nierprobleme, insluitende nierversaking. U dokter mag bloedtoetse uitvoer om te sien of u niere korrek funksioneer.
- Koors, kouekoors, seer keel, hoes of ander tekens van infeksie.
- Psigiatriese simptome insluitende verwardheid, erge depressie, selfmoordgedagtes, uitermatige vrees, hallusinasies of ongewone gedrag.
- Koors met erge blaasvorming, afskilfering en rooi veluitslag of enige erge velreaksie.
- Stuiptrekkings.

Lig u dokter in as u enige van die volgende newe-effekte ondervind of as enige van hierdie simptome lastig is of nie verdwyn nie:
- Gewigstoename of –verlies.
- Duiseligheid.
- Gevoelloosheid, prikkeling, naalde en spelde.
- Bewerasie.
- Moeite met konsentrasie.
- Lomerigheid.
- Moeite om aan die slaap te raak.
- Ongewone drome.
- Hoofpyn.
- Afwykings van koördinasie en balans.
- Vergeetagtigheid.
- Verwardheid.
- Abnormale euforie
- 'n gevoel van depressie en angs
- Onduidelike gesig.
- Oorsuising en 'n draaigevoel (vertigo).
- Sinusitis
- Hartkloppings (vinnig en ongereeld).
- Versnelling van die pols.
- Asma.
- Naarheid, braking.
- Diaree en hardlywigheid.
- Maagpyn.
- Indigestie.
- Omgekrapte maag.
- Toename in eetlus.
- Verlies aan eetlus.
- Smaakafwykings.
- Inflammasie van die pankreas (erge buikpyn).
- Veluitslag.
- Jeuk.
- Toename in sweet.
- Ekseem.
- Haarverlies.
- Aknee.
- Vertanderinge in vel- en naelkleur.
- Spier- of gewrigspyn.
- Impotensie (verlies aan manlike funksionering); toename en afname in geslagsdrang (libido).
- Moegheid en tekort aan energie.
- Warmgloede.
- Griepagtige simptome.
- Algemene gevoel van ongesteldheid.
- Pyn, rugpyn, borspyn.
- Kortademheid.
- Hoes.
- Loop- of verstopte neus.
- Borsvergroting in mans.
- Bloed in die uriene, inflammasie van die niere, dikwelse urienlating en dors.
- Verandering in die vorm of plek van vetneerlegging (veral in u arms, bene, gesig, nek, borste en heupe).

Bloedtoetse mag ook die volgende toon:
- Afname van fosfaatvlakke in die bloed.
- Toename in die vlakke van kreatienkinase in die bloed wat tot spierpyn en –swakheid mag lei.
- Anemie (lae rooibloedseltelling).
- Lae witbloedseltelling (dit mag lei tot 'n groter waarskynlikheid vir infeksie).
- Toename in vetsure (trigliseriede, bilirubien- of suikervlakke in die bloed.
- Lewer- en pankreasprobleme.
- Afname van kalium in die bloed.
- Toename van kreatinien in die bloed.
- Proteïen in die uriene.

> **Nie al die newe-effekte wat vir TRIOLAR TABLETTE aangemeld is, word in hierdie blaadjie genoem nie. As u algemene gesondheid agteruitgaan terwyl u TRIOLAR TABLETTE neem, moet u asseblief u dokter, apteker of ander gesondheidsorgbeampte vir advies raadpleeg.**

BERGING EN WEGDOEN VAN TRIOLAR TABLETTE
Bewaar by of onder 25 °C (kamertemperatuur). Hou die HDPE houers dig toe.

HOU ALLE MEDISYNE BUITE BEREIK EN SIG VAN KINDERS

> Neem alle ongebruikte medisyne na u apteker terug.
> Moenie van ongebruikte medisyne in die riolerinsgsisteem (bv. toilet) ontslae raak nie.

AANBIEDING:
TRIOLAR TABLETTE
HDPE Houer:
Tablette word in 'n wit, ondeurskynende, ronde 120 ml HDPE houer met 'n 38 mm nek en 38 mm wit, ondeurskynende polipropileen geribde deksel en prop met induksiegeseëlde voering geseël. Elke houer bevat 28 of 30 tablette.

IDENTIFIKASIE
TRIOLAR TABLETTE
Pienk, kapsulevormige, bikonvekse, filmbedekte tablette met "CL 81" op die een kant gedruk.

REGISTRASIENOMMER:
47/20.2.8/1006.

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